```
=> fil reg

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STRUCTURE FILE UPDATES:   11 OCT 2004  HIGHEST RN 760932-70-5
DICTIONARY FILE UPDATES:  11 OCT 2004  HIGHEST RN 760932-70-5

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

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  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

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information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d que l6
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/RN


=> d ide

L6   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   300832-84-2  REGISTRY
CN   Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic
     acid, 6-[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16
     ,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-
     4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI)  (CA
     INDEX NAME)
OTHER NAMES:
CN   BILN 2061
CN   BILN 2061ZW
CN   Ciluprevir
FS   STEREOSEARCH
MF   C40 H50 N6 O8 S
SR   CA
LC   STN Files:   ADISINSIGHT, CA, CAPLUS, IMSRESEARCH, PHAR, PROUSDDR,
       TOXCENTER, USPATFULL
DT.CA  CAplus document type:  Journal; Patent
RL.P   Roles from patents:  BIOL (Biological study); PREP (Preparation); PROC
       (Process); RACT (Reactant or reagent); USES (Uses)
RL.NP  Roles from non-patents:  BIOL (Biological study); PREP (Preparation);
       PRP (Properties); USES (Uses)

Absolute stereochemistry.
Double bond geometry as shown.
```
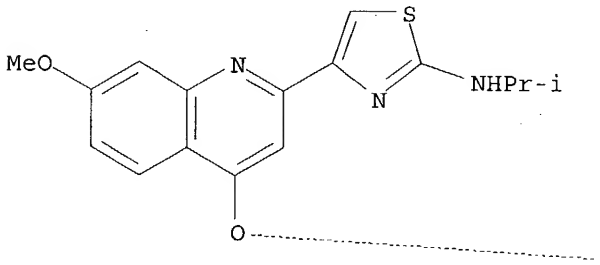
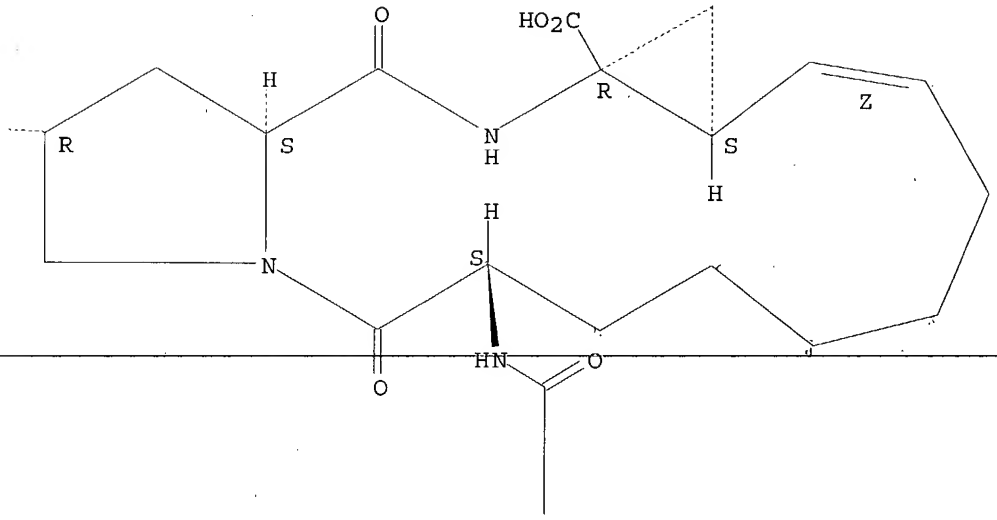
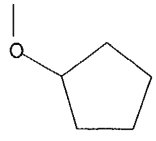

PAGE 1-A



PAGE 1-B



PAGE 2-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

15 REFERENCES IN FILE CA (1907 TO DATE)
15 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> FIL STNGUIDE

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=> => fil reg

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DICTIONARY FILE UPDATES: 11 OCT 2004 HIGHEST RN 760932-70-5

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when
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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
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http://www.cas.org/ONLINE/DBSS/registryss.html

=> fil hcap

FILE 'HCAPLUS' ENTERED AT 12:19:27 ON 13 OCT 2004
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FILE COVERS 1907 - 13 Oct 2004 VOL 141 ISS 16
FILE LAST UPDATED: 12 Oct 2004 (20041012/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

```
=> fil medlin

FILE 'MEDLINE' ENTERED AT 12:19:32 ON 13 OCT 2004

 FILE LAST UPDATED: 12 OCT 2004 (20041012/UP). FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> fil embase

FILE 'EMBASE' ENTERED AT 12:19:35 ON 13 OCT 2004
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 FILE COVERS 1974 TO 7 Oct 2004 (20041007/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

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=> fil biosis

FILE 'BIOSIS' ENTERED AT 12:19:38 ON 13 OCT 2004
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 6 October 2004 (20041006/ED)

FILE RELOADED: 19 October 2003.

=> fil adisinsight

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FILE COVERS 1986 TO 7 Oct 2004 (20041007/ED)
FILE LAST UPDATED: 7 OCT 2004 (20041007/ED)

=> fil imsresearch

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FILE COVERS 1977 TO 8 Oct 2004 (20041008/ED)

 ###################################################################
 #                                                                 #
```

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The file name DRUGUPDATES is now an alias for IMSRESEARCH.

=> fil phar

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FILE RELOADED May 4, 2003
FILE LAST UPDATED: Oct 8, 2004 (20041008/ED)

PHAR was reloaded and enhanced with pharmacokinetic information and systematic chemical names. Enter HELP RLOAD at an arrow prompt in PHAR for the reload information.

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=> fil toxcenter

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FILE COVERS 1907 TO 5 Oct 2004 (20041005/ED)

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TOXCENTER has been enhanced with new files segments and search fields.
See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

=> fil uspatfull

FILE 'USPATFULL' ENTERED AT 12:20:12 ON 13 OCT 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 12 Oct 2004 (20041012/PD)
FILE LAST UPDATED: 12 Oct 2004 (20041012/ED)
HIGHEST GRANTED PATENT NUMBER: US6804828
HIGHEST APPLICATION PUBLICATION NUMBER: US2004199971
CA INDEXING IS CURRENT THROUGH 12 Oct 2004 (20041012/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 12 Oct 2004 (20041012/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2004

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

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=> fil wpix

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FILE LAST UPDATED: 11 OCT 2004 <20041011/UP>
MOST RECENT DERWENT UPDATE: 200465 <200465/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
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    http://thomsonderwent.com/support/userguides/                <<<

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    DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
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    HIT STRUCTURES WITHIN THE BIBLIOGRAPHIC DOCUMENT  <<<

=> file stnguide

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LAST RELOADED: Oct  8, 2004 (20041008/UP).

=> d que l15
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/RN
L7             0 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/CRN
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L6 OR L7)
L9            15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8
L10            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  300832-84-2D?
L11           15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9 OR L10
L12               SEL  PLU=ON  L8 1- CHEM :        4 TERMS
L13           17 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12
L14            6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  300832-84-2P
L15           17 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L9 OR L10 OR L11) OR (L13 OR
                  L14)


=>

     (FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 12:01:12 ON 13 OCT 2004)


=> d que l26
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/RN
L7             0 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/CRN
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L6 OR L7)
L16               SEL  PLU=ON  L8 1- CHEM :        4 TERMS
L17           74 SEA L16
L18       345253 SEA ?CRYST?
L19      1408058 SEA ?PHASE? OR ?PHASIC?
L20      2861999 SEA ?MORPH?
L21      1578978 SEA FORM
L22            8 SEA L17 (L) (L18 OR L19 OR L20 OR L21)
L23      4478959 SEA ?STRUCTUR?
L24           11 SEA L17 (L) L23
L25           16 SEA L22 OR L24
L26            8 DUP REM L25 (8 DUPLICATES REMOVED)


=>
     (FILE 'ADISINSIGHT, IMSRESEARCH, PHAR, TOXCENTER' ENTERED AT 12:07:26 ON
     13 OCT 2004)
```

L20 — picked up "morphine"

```
=> d que l29
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/RN
L7             0 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/CRN
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L6 OR L7)
L27              SEL  PLU=ON  L8 1- CHEM :       4 TERMS
L28           12 SEA L27
L29           12 DUP REM L28 (0 DUPLICATES REMOVED)


=> d que l31
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/RN
L7             0 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/CRN
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L6 OR L7)
L30              SEL  PLU=ON  L8 1- CHEM :       4 TERMS
L31            6 SEA FILE=USPATFULL ABB=ON  PLU=ON  L30


=> d que l40
L35            2 SEA FILE=WPIX ABB=ON  PLU=ON  (BILN-2061/BIX OR CILUPREVIR/BIX)

L36            2 SEA FILE=WPIX ABB=ON  PLU=ON  (BILN(1W)2061 OR ?CILUPREV IR OR
                 ?CILU PREVIR? OR CI LUPREVIR?)/BIX
L37            2 SEA FILE=WPIX ABB=ON  PLU=ON  (L35 OR L36)
L38            0 SEA FILE=WPIX ABB=ON  PLU=ON  L37 AND ?CRYST?
L39            0 SEA FILE=WPIX ABB=ON  PLU=ON  L37 AND ?CRYST?/BIX
L40            2 SEA FILE=WPIX ABB=ON  PLU=ON  (L37 OR L38 OR L39)


=> dup rem l15 l26 l29 l31 l40
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, IMSRESEARCH, PHAR'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE

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PROCESSING COMPLETED FOR L15
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```
PROCESSING COMPLETED FOR L26
PROCESSING COMPLETED FOR L29
PROCESSING COMPLETED FOR L31
PROCESSING COMPLETED FOR L40
L41          36 DUP REM L15 L26 L29 L31 L40 (9 DUPLICATES REMOVED)
                ANSWERS '1-17' FROM FILE HCAPLUS
                ANSWERS '18-19' FROM FILE MEDLINE
                ANSWERS '20-22' FROM FILE BIOSIS
                ANSWERS '23-25' FROM FILE ADISINSIGHT
                ANSWERS '26-27' FROM FILE IMSRESEARCH
                ANSWERS '28-29' FROM FILE PHAR
                ANSWERS '30-31' FROM FILE TOXCENTER
                ANSWERS '32-36' FROM FILE USPATFULL

=> d iall retable

L41  ANSWER 1 OF 36  HCAPLUS  COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2004:310970  HCAPLUS
DOCUMENT NUMBER:          140:327091
ENTRY DATE:               Entered STN:  16 Apr 2004
TITLE:                    Potent inhibitor of HCV serine protease
INVENTOR(S):              Chen, Shirlynn; Nehmiz, Gerhard; Croenlein, Jens
                          Oliver; Steinmann, Gerhard; Gunn, Jocelyn Abella;
                          Costa, Phuong Do
PATENT ASSIGNEE(S):       Boehringer Ingelheim International G.m.b.H., Germany
SOURCE:                   PCT Int. Appl., 42 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
INT. PATENT CLASSIF.:
            MAIN:         A61K031-4709
       SECONDARY:         A61K045-06; A61P031-14
CLASSIFICATION:           63-6 (Pharmaceuticals)
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     --------------       ----   --------    --------------------     --------
     WO 2004030670         A1    20040415    WO 2003-US30402          20030925
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
             GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
             LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
             OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
             TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
             NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
             GW, ML, MR, NE, SN, TD, TG
     US 2004138109         A1    20040715    US 2003-663220           20030916
PRIORITY APPLN. INFO.:                       US 2002-414940P      P   20020930
                                             US 2002-421904P      P   20021029
                                             US 2002-433834P      P   20021216
                                             US 2003-443662P      P   20030130

PATENT CLASSIFICATION CODES:
 PATENT NO.        CLASS  PATENT FAMILY CLASSIFICATION CODES
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 WO 2004030670     ICM    A61K031-4709
                   ICS    A61K045-06; A61P031-14
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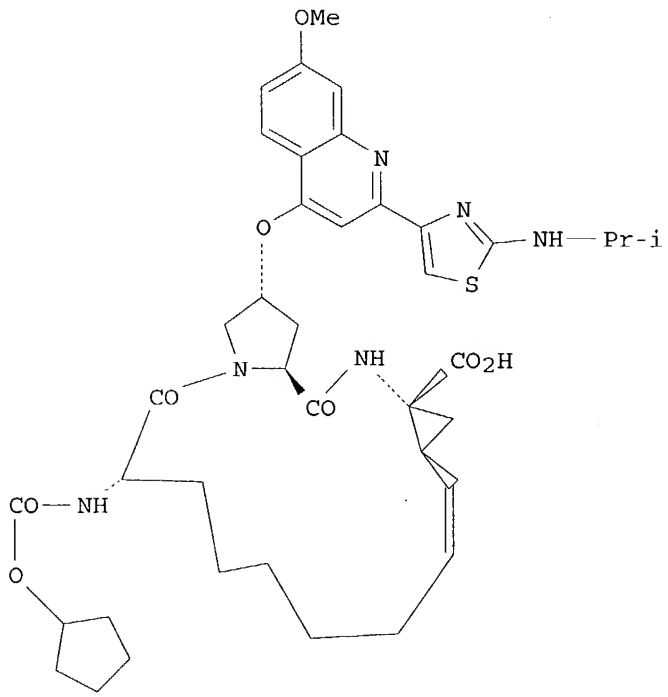

I

ABSTRACT:
Disclosed are oral pharmaceutical compns., kits and methods of treating and preventing Hepatitis C Viral (HCV) infections wherein Compound (I), a potent inhibitor of HCV serine protease, or a pharmaceutically acceptable salt thereof, is administered in a selected dosage range. Also disclosed are the use of I or a pharmaceutically acceptable salt thereof, as a control substance for validating an HCV replication assay and also as a control substance for determining the relative effectiveness of one or more substances, alone or in combination, to inhibit the replication of HCV.

SUPPL. TERM: HCV serine proteinase inhibitor
INDEX TERM: Drug delivery systems
(carriers; potent inhibitor of HCV serine protease)
INDEX TERM: Cytoprotective agents
(hepatoprotective; potent inhibitor of HCV serine protease)
INDEX TERM: Hepatitis A virus
Hepatitis B virus
Human immunodeficiency virus
(inhibitors; potent inhibitor of HCV serine protease)
INDEX TERM: Antiviral agents
Hepatitis C virus
Human
Immunomodulators
Solvents
(potent inhibitor of HCV serine protease)
INDEX TERM: Polyoxyalkylenes, biological studies

ROLE: NUU (Other use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solvent; potent inhibitor of HCV serine protease)

INDEX TERM: 37259-58-8, Serine proteinase
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(HCV, inhibitors; potent inhibitor of HCV serine protease)

INDEX TERM: **300832-84-2**
ROLE: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(potent inhibitor of HCV serine protease)

INDEX TERM: 57-55-6, Propylene glycol, biological studies 64-17-5, Ethanol, biological studies 7732-18-5, Water, biological studies 25322-68-3, Polyethylene glycol
ROLE: NUU (Other use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solvent; potent inhibitor of HCV serine protease)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S):
(1) Anon; CURRENT DRUG DISCOVERY 2002, P45
(2) Boehringer Ingelheim Ca Ltd; WO 0059929 A 2000 HCAPLUS
(3) Boehringer Ingelheim Pharma; WO 03066103 A 2003 HCAPLUS

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	2002		45	CURRENT DRUG DISCOVE	
Boehringer Ingelheim Ca	2000			WO 0059929 A	HCAPLUS
Boehringer Ingelheim Ph	2003			WO 03066103 A	HCAPLUS

=> d iall retable 2-17

L41 ANSWER 2 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:142968 HCAPLUS
DOCUMENT NUMBER: 140:193056
ENTRY DATE: Entered STN: 22 Feb 2004
TITLE: Combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compositions, and use in the treatment of cytokine-mediated diseases
INVENTOR(S): Simianer, Stefan; Bilbault, Pascal; Cappola, Michael L.; Way, Susan Lynn
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA; Boehringer Ingelheim France
SOURCE: PCT Int. Appl., 168 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K031-5377
SECONDARY: A61K031-505; A61K031-42; A61K039-395; A61K031-427; A61K031-506; A61P001-00; A61P017-06; A61P019-02
CLASSIFICATION: 1-7 (Pharmacology)
Section cross-reference(s): 28, 63
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014387	A1	20040219	WO 2003-US25341	20030812
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004110755	A1	20040610	US 2003-638702	20030811
PRIORITY APPLN. INFO.:			US 2002-403115P P	20020813

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004014387	ICM	A61K031-5377
	ICS	A61K031-505; A61K031-42; A61K039-395; A61K031-427; A61K031-506; A61P001-00; A61P017-06; A61P019-02

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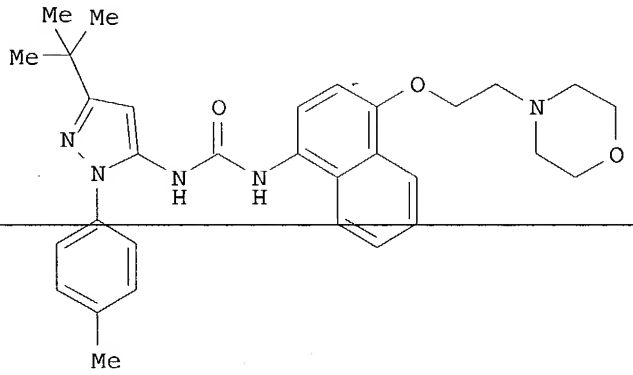

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ABSTRACT:
The invention relates to pharmaceutical combination therapies based on p38 kinase inhibitors and another active ingredients, pharmaceutical compns. comprising such combinations, processes for preparing them, and their use in the treatment of cytokine-mediated diseases. Preparation of I (BIRB 796 BS) is described.

SUPPL. TERM: cytokine disease therapeutic p38 MAP kinase inhibitor combination; BIRB 796 BS prepn p38 MAP kinase inhibitor

INDEX TERM: Fusion proteins (chimeric proteins)
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CTLA4-Ig; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Intestine, disease
(Crohn's; combinations of active agents with p38 MAP

kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Selectins
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(E-, inhibitors; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Cell adhesion molecules
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(ICAM-1 (intercellular adhesion mol. 1), inhibitors; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Interleukin 1 receptors
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: CD4 (antigen)
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-CD4; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: CD80 (antigen)
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-CD80; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Antibodies and Immunoglobulins
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-LFA3-IgC1; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Drugs
(biol. agents; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Angiogenesis inhibitors
Antirheumatic agents
Antiviral agents
Cytotoxic agents
Drug delivery systems
Human
Immunomodulators
Immunosuppressants
Photodynamic therapy
Phototherapy
Psoriasis
Rheumatoid arthritis
UV A radiation
UV B radiation
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: CTLA-4 (antigen)
Cytokines
Interleukin 10
Interleukin 6
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Antibodies and Immunoglobulins
Glucocorticoids
Macrolides
Retinoids
Steroids, biological studies
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Fusion proteins (chimeric proteins)
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphtheria toxin fragment DAB389; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Fusion proteins (chimeric proteins)
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphtheria toxin; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Toxins
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphtheria, DAB389, fusion products; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Toxins
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(diphtheria, DAB389; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Toxins
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphtheria, fusion products; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Interleukin 2
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fusion products; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Antibodies and Immunoglobulins
ROLE: PAC (Pharmacological activity); THU (Therapeutic use);

BIOL (Biological study); USES (Uses)
(fusion protein with CTLA-4; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: CTLA-4 (antigen)
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fusion protein with Ig; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Drugs
(gastrointestinal; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Cell adhesion molecules
LFA-1 (antigen)
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Anti-inflammatory agents
(nonsteroidal; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Drug delivery systems
(tablets; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Interleukin 2 receptors
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(α chain, anti-CD25; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Interferons
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: Interferons
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β, β1B; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 7631-86-9, Silicon Dioxide, biological studies
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Colloidal; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 9004-34-6, Cellulose, biological studies
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Microcryst.; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 9005-25-8, Starch, biological studies
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Pregelatinized; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 127464-60-2, Vascular endothelial growth factor
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(agents against; combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 80295-53-0, Complement c5 106362-32-7, Peptide T
165245-96-5, p38 Kinase
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 285983-48-4P, BIRB 796BS
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 50-02-2, Dexamethasone 50-18-0, Cyclophosphamide
50-24-8, Prednisolone 50-35-1, Thalidomide 50-44-2, Mercaptopurine 50-78-2, Aspirin 52-67-5, D-Penicillamine
53-86-1, Indomethacin 54-21-7, Sodium salicylate
59-05-2, Methotrexate 61-68-7, Mefenamic acid 67-97-0D, Vitamin D3, analogs 80-08-0, Dapsone 83-43-2, Methylprednisolone 89-57-6, 5-ASA 103-90-2, Acetaminophen 118-42-3, Hydroxychloroquine 305-03-3, Chlorambucil 378-44-9, Betamethasone 446-86-6, Azathioprine 552-94-3, Salsalate 599-79-1, Sulfasalazine
1406-16-2, Vitamin D 2016-36-6, Choline salicylate, biological studies 3615-24-5, Ramifenazone 5104-49-4, Flurbiprofen 6385-02-0, Meclofenamate sodium 6493-05-6
10118-90-8, Minocycline 12244-57-4, Gold sodium thiomalate
14484-47-0, Deflazacort 15307-86-5, Diclofenac
15687-27-1, Ibuprofen 18917-89-0, Magnesium salicylate
21256-18-8, Oxaprozin 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22494-42-4, Diflunisal 23187-87-3, Choline magnesiumsalicylate 26171-23-3, Tolmetin 31842-01-0, Indoprofen 33005-95-7, Tiaprofenic acid 33069-62-4, Taxol 34031-32-8, Auranofin 34597-40-5, Fenoprofen calcium 36322-90-4, Piroxicam 38194-50-2, Sulindac
41340-25-4, Etodolac 42924-53-8, Nabumetone 51333-22-3, Budesonide 51803-78-2, Nimesulide 53123-88-9, Sirolimus
53716-49-7, Carprofen 59865-13-3, Cyclosporine
70374-39-9, Lornoxicam 71125-38-7, Meloxicam 74103-07-4, Ketorolac tromethamine 75706-12-6, Leflunomide
80937-31-1, Flosulide 104987-11-3, Tacrolimus
104987-12-4, Ascomycin 128794-94-5, Mycophenolate mofetil
137071-32-0, Pimecrolimus 152923-56-3, Daclizumab
156679-34-4, Ro 45-2081 162011-90-7, Rofecoxib
169590-42-5, Celecoxib 170277-31-3, Infliximab
179045-86-4, Basiliximab 181695-72-7, Valdecoxib
185243-69-0, Etanercept 189261-10-7, Antegren

202409-33-4, Etoricoxib 214745-43-4, Efalizumab
222535-22-0, Alefacept 294848-51-4 294848-58-1
294849-20-0 294849-84-6 294850-04-7 294850-87-6
294851-64-2 **300832-84-2** 321656-57-9
331257-52-4, ISIS 2302 331731-18-1, Adalimumab
336128-48-4, CDP 571 662151-94-2, ISIS 8
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 605-62-9, 4-Nitro-1-hydroxynaphthalene 637-60-5, p-Tolylhydrazine hydrochloride 3647-69-6, 4-(2-Chloroethyl)morpholine hydrochloride 17341-93-4, 2,2,2-Trichloroethyl chloroformate 59997-51-2, Pivaloylacetonitrile 317806-90-9
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 317806-86-3P 317806-87-4P 317806-88-5P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 317806-89-6P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

INDEX TERM: 66-97-7D, Psoralen, derivs. 557-04-0, Magnesium Stearate 9003-39-8, Povidone K30 9063-38-1, Sodium StarchGlycolate 64044-51-5, Lactose Monohydrate
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S):
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RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	2002	46	328	ARTHRITIS AND RHEUMA	
Anon	2000	10	1951	EXPERT OPINION ON TH	
Boehringer Ingelheim Ph	2002			WO 0207772 A	HCAPLUS
Hatoum-Makdad, H	2003			WO 03068223 A	HCAPLUS
Madwed, J	2001	50	S175	IMFLAMMATION RESEARC	

Madwed, J	2001	50	S184	IMFLAMMATION RESEARC	
Smithkline Beecham Corp	2001			WO 0137837 A	HCAPLUS

L41 ANSWER 3 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:252197 HCAPLUS
DOCUMENT NUMBER: 140:281350
ENTRY DATE: Entered STN: 26 Mar 2004
TITLE: Spiro compounds for inhibiting the first-pass effect
INVENTOR(S): Harris, James W.
PATENT ASSIGNEE(S): Bioavailability System, LLC, USA
SOURCE: U.S. Pat. Appl. Publ., 133 pp., Cont.-in-part of U.S. Ser. No. 793,416.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K031-353
US PATENT CLASSIF.: 514453000
CLASSIFICATION: 1-2 (Pharmacology)
Section cross-reference(s): 28, 63
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004058982	A1	20040325	US 2003-422848		20030425
US 6248776	B1	20010619	US 1999-251467		19990217
US 6476066	B1	20021105	US 2001-793416		20010227
PRIORITY APPLN. INFO.:			US 1999-251467	A3	19990217
			US 2001-793416	A2	20010227
			US 1997-56382P	P	19970826
			US 1997-997259	A2	19971223

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004058982	ICM	A61K031-353
	NCL	514453000
US 2004058982	ECLA	A23L001/30B; A23L002/06; A23L002/39; A61K031/352; A61K031/37; A61K035/78
US 6476066	ECLA	A23L001/30B; A23L002/06; A23L002/39; A61K031/35P; A61K031/37; A61K035/78; C07D493/10; C07D519/00

OTHER SOURCE(S): MARPAT 140:281350
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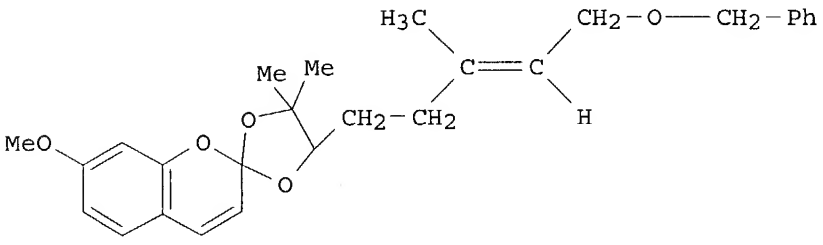

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ABSTRACT:
Compns., methods, etc. for addressing the first-pass effect are presented. An example compound prepared was I. Also processing citrus oils to obtain the compds.

is given as examples as well as assessment of human cytochrome P 450-mediated biotransformation.

SUPPL. TERM: spiro compd first pass metab inhibition
INDEX TERM: Essential oils
ROLE: PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(citrus; spiro compds. for inhibiting the first-pass effect)
INDEX TERM: Drug delivery systems
(oral; spiro compds. for inhibiting the first-pass effect)
INDEX TERM: Human
Metabolism, animal
(spiro compds. for inhibiting the first-pass effect)
INDEX TERM: 674773-16-1P
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(spiro compds. for inhibiting the first-pass effect)
INDEX TERM: 531-59-9, 7-Methoxycoumarin 55776-46-0, Benzyl 6,7-epoxygeranyl ether
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(spiro compds. for inhibiting the first-pass effect)
INDEX TERM: 33069-62-4, Paclitaxel 114977-28-5, Docetaxel 127779-20-8, Saquinavir 161814-49-9, Amprenavir 174484-41-4, Tipranavir 206361-99-1, TMC114 226700-80-7, VX 175 **300832-84-2, BILN 2061** 461443-59-4 479543-46-9, VX-702 569364-34-7, VX-950 675184-03-9, VX 385 675184-27-7, HCV 371 675184-41-5, VP 50406
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(spiro compds. for inhibiting the first-pass effect)

L41 ANSWER 4 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2004:325457 HCAPLUS
DOCUMENT NUMBER: 141:16899
ENTRY DATE: Entered STN: 22 Apr 2004
TITLE: In Vitro Resistance Studies of Hepatitis C Virus Serine Protease Inhibitors, VX-950 and **BILN 2061**: structural analysis indicates different resistance mechanisms
AUTHOR(S): Lin, Chao; Lin, Kai; Luong, Yu-Ping; Rao, B. Govinda; Wei, Yun-Yi; Brennan, Debra L.; Fulghum, John R.; Hsiao, Hsun-Mei; Ma, Sue; Maxwell, John P.; Cottrell, Kevin M.; Perni, Robert B.; Gates, Cynthia A.; Kwong, Ann D.
CORPORATE SOURCE: Vertex Pharmaceuticals Inc., Cambridge, MA, 02139, USA
SOURCE: Journal of Biological Chemistry (2004), 279(17), 17508-17514
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-3 (Pharmacology)
ABSTRACT:
We have used a structure-based drug design approach to identify small mol.

inhibitors of the hepatitis C virus (HCV) NS3·4A protease as potential candidates for new anti-HCV therapies. VX-950 is a potent NS3·4A protease inhibitor that was recently selected as a clin. development candidate for hepatitis C treatment. In this report, we describe in vitro resistance studies using a subgenomic replicon system to compare VX-950 with another HCV NS3·4A protease inhibitor, **BILN 2061**, for which the Phase I clin. trial results were reported recently. Distinct drug-resistant substitutions of a single amino acid were identified in the HCV NS3 serine protease domain for both inhibitors. The resistance conferred by these mutations was confirmed by characterization of the mutant enzymes and replicon cells that contain the single amino acid substitutions. The major **BILN** ***2061*** -resistant mutations at Asp168 are fully susceptible to VX-950, and the dominant resistant mutation against VX-950 at Ala156 remains sensitive to ***BILN*** **2061.** Modeling anal. suggests that there are different mechanisms of resistance to VX-950 and **BILN 2061.**

SUPPL. TERM: hepatitis C virus serine protease antiviral resistance VX950 BILN2061

INDEX TERM: Drug resistance
Structure-activity relationship
(antiviral; structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

INDEX TERM: Antiviral agents
(resistance to; structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

INDEX TERM: Antiviral agents
Hepatitis C virus
Molecular modeling
(structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

INDEX TERM: Viral RNA
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

INDEX TERM: 56-41-7, L-Alanine, biological studies 70-47-3, L-Asparagine, biological studies
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(mutation; structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

INDEX TERM: 149885-80-3, NS3 serine protease
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

INDEX TERM: **300832-84-2, BILN 2061**
569364-34-7, VX-950
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-activity relationship and in vitro antiviral

resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and **BILN 2061**)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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Alter, H	2000	20	17	Semin Liver Dis	MEDLINE
Babine, R	2002			WO 0218369	HCAPLUS
Bartenschlager, R	1993	67	3835	J Virol	HCAPLUS
Bartenschlager, R	1995	69	7519	J Virol	HCAPLUS
Blight, K	1998	3	71	Antiviral Ther	MEDLINE
Blight, K	2000	290	1972	Science	HCAPLUS
Chander, G	2002	36	S135	Hepatology	

Davis, G	1998	339	1493	N Engl J Med	HCAPLUS
De Francesco, R	2003	58	1	Antiviral Res	HCAPLUS
Di Marco, S	2000	275	7152	J Biol Chem	HCAPLUS
Failla, C	1995	69	1769	J Virol	HCAPLUS
Grakoui, A	1993	67	1385	J Virol	HCAPLUS
Grakoui, A	1993	67	2832	J Virol	HCAPLUS
Hijikata, M	1993	90	10773	Proc Natl Acad Sci U	HCAPLUS
Hirsch, M	2003	37	113	Clin Infect Dis	
Kenny-Walsh, E	2001	5	969	Clin Liver Dis	MEDLINE
Kim, J	1996	87	343	Cell	HCAPLUS
Kolykhalov, A	2000	74	2046	J Virol	HCAPLUS
Lai, C	2003	36	687	Clin Infect Dis	HCAPLUS
Lamarre, D	2003	426	186	Nature	HCAPLUS
Landro, J	1997	36	9340	Biochemistry	HCAPLUS
Lin, C	1995	69	4373	J Virol	HCAPLUS
Lin, C	1995	92	7622	Proc Natl Acad Sci U	HCAPLUS
Lohmann, V	2001	75	1437	J Virol	HCAPLUS
Lohmann, V	1999	285	110	Science	HCAPLUS
Love, R	1996	87	331	Cell	HCAPLUS
McHutchison, J	1998	339	1485	N Engl J Med	HCAPLUS
Migliaccio, G	2003	278	49164	J Biol Chem	HCAPLUS
Morrison, J	1969	185	269	Biochim Biophys Acta	HCAPLUS
Neumann, A	1998	282	103	Science	HCAPLUS
Nguyen, T	2003	47	3525	Antimicrob Agents Ch	HCAPLUS
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Taliani, M	1997	240	60	Anal Biochem	
Tanji, Y	1995	69	1575	J Virol	HCAPLUS
Tomei, L	1993	67	4017	J Virol	HCAPLUS
Trozzi, C	2003	77	3669	J Virol	HCAPLUS
Tsantrizos, Y	2003	42	1356	Angew Chem Int Ed En	HCAPLUS
Wasley, A	2000	20	1	Semin Liver Dis	MEDLINE
Yao, N	1999	7	1353	Struct Fold Des	HCAPLUS

L41 ANSWER 5 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2004:468978 HCAPLUS
DOCUMENT NUMBER: 141:220806
ENTRY DATE: Entered STN: 10 Jun 2004
TITLE: Mutations conferring resistance to a potent hepatitis C virus serine protease inhibitor in vitro
AUTHOR(S): Lu, Liangjun; Pilot-Matias, Tami J.; Stewart, Kent D.; Randolph, John T.; Pithawalla, Ron; He, Wenping; Huang, Peggy P.; Klein, Larry L.; Mo, Hongmei; Molla, Akhteruzzaman
CORPORATE SOURCE: Antiviral Research, Global Pharmaceutical Research and Development, Abbott Park, IL, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2004), 48(6), 2260-2266
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 7-5 (Enzymes)
Section cross-reference(s): 1, 10

ABSTRACT:

BILN 2061 is a novel, specific hepatitis C virus (HCV) NS3 serine protease inhibitor discovered by Boehringer Ingelheim that has shown potent activity against HCV replicons in tissue culture and is currently under clin. investigation for the treatment of HCV infection. The poor fidelity of the HCV RNA-dependent RNA polymerase will likely lead to the development of

drug-resistant viruses in treated patients. The development of resistance to ***BILN*** **2061** was studied by the in vitro passage of HCV genotype 1b replicon cells in the presence of a fixed concentration of the drug. Three weeks posttreatment, four colonies were expanded for genotypic and phenotypic characterization. The 50% inhibitory concns. of **BILN 2061** for these colonies were 72- to 1228-fold higher than that for the wild-type replicon. Sequencing of the individual colonies identified several mutations in the NS3 serine protease gene. Mol. clones containing the single amino acid substitution A156T, R155Q, or D168V resulted in 357-fold, 24-fold, and 144-fold redns. in susceptibility to **BILN 2061**, resp., compared to the level of susceptibility shown by the wild-type replicon. Modeling studies indicate that all three of these residues are located in close proximity to the inhibitor binding site. These findings, in addition to the three-dimensional structure anal. of the NS3/NS4A serine protease inhibitor complex, provide a strategic guide for the development of next-generation inhibitors of HCV NS3/NS4A serine protease.

SUPPL. TERM: NS3 protease mutation **BILN 2061**
hepatitis C virus

INDEX TERM: Drug resistance
(antiviral; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: Hepatitis C virus
(genotype 1b; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: Enzyme functional sites
(inhibitor-binding; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: Conformation
Mutation
(mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: Replicon
(of hepatitis C virus; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: 74-79-3, L-Arginine, biological studies
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(155; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: 56-41-7, L-Alanine, biological studies
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(156; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: 56-84-8, L-Aspartic acid, biological studies
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(168; mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: 259216-22-3 259216-62-1 **300832-84-2**, **BILN 2061**
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(mutations conferring inhibitor resistance on hepatitis C virus serine protease)

INDEX TERM: 149885-80-3, NS3-NS4A protease
ROLE: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(wild type and mutant forms; mutations conferring

inhibitor resistance on hepatitis C virus serine protease)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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Barbato, G	1999	289	371	J Mol Biol	HCAPLUS
Bartenschlager, R	1999	6	165	J Viral Hepat	MEDLINE
Bartenschlager, R	1994	68	5045	J Virol	HCAPLUS
Boehringer Ingelheim (C	2003			US 6534523 B1	HCAPLUS
Boehringer Ingelheim (C	2003			US 6608027 B1	HCAPLUS
Cicero, D	1999	289	385	J Mol Biol	HCAPLUS
Cornberg, M	2002	4	23	Curr Gastroenterol R	
De Francesco, R	2002			WO 0259321	
Di Marco, S	2000	275	7152	J Biol Chem	HCAPLUS
Failla, C	1995	69	1769	J Virol	HCAPLUS
Foy, E	2003	300	1145	Science	HCAPLUS
Grakoui, A	1993	67	1385	J Virol	HCAPLUS

Ikeda, M	2002	76	2997	J Virol	HCAPLUS
Kolykhalov, A	2000	74	2046	J Virol	HCAPLUS
Krieger, N	2001	75	4614	J Virol	HCAPLUS
Lamarre, D	2003	426	186	Nature	HCAPLUS
Llinas-Brunet, M	1998	8	1713	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2000	10	2267	Bioorg Med Chem Lett	HCAPLUS
Lohmann, V	2001	75	1437	J Virol	HCAPLUS
Mo, H	2003	59	173	Antivir Res	HCAPLUS
Molla, A	1996	2	760	Nat Med	HCAPLUS
Narjes, F	2003	12	153	Expert Opin Investig	HCAPLUS
Neddermann, P	1997	378	469	Biol Chem	HCAPLUS
Pauwels, R	1988	20	309	J Virol Methods	HCAPLUS
Pizzi, E	1994	91	888	Proc Natl Acad Sci U	HCAPLUS
Steinkuhler, C	2001	8	919	Curr Med Chem	HCAPLUS
Trozzi, C	2003	77	3669	J Virol	HCAPLUS
Tsantrizos, Y	2003	42	1356	Angew Chem Int Ed En	HCAPLUS
Wright, M	2001	12	201	Antivir Chem Chemoth	HCAPLUS
Yan, Y	1998	7	837	Protein Sci	HCAPLUS
Yao, N	1999	7	1353	Struct Fold Des	HCAPLUS
Yi, M	2002	304	197	Virology	HCAPLUS

L41 ANSWER 6 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2004:168624 HCAPLUS
DOCUMENT NUMBER: 140:350045
ENTRY DATE: Entered STN: 02 Mar 2004
TITLE: Structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**
AUTHOR(S): Llinas-Brunet, Montse; Bailey, Murray D.; Bolger, Gordon; Brochu, Christian; Faucher, Anne-Marie; Ferland, Jean Marie; Garneau, Michel; Ghiro, Elise; Gorys, Vida; Grand-Maitre, Chantal; Halmos, Ted; Lapeyre-Paquette, Nicole; Liard, Francine; Poirier, Martin; Rheaume, Manon; Tsantrizos, Youla S.; Lamarre, Daniel
CORPORATE SOURCE: Departments of Chemistry and Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Journal of Medicinal Chemistry (2004), 47(7), 1605-1608
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-3 (Pharmacology)
Section cross-reference(s): 34

ABSTRACT:
From the discovery of competitive hexapeptide inhibitors, potent and selective HCV NS3 protease macrocyclic inhibitors have been identified. Structure-activity relationship studies were performed focusing on optimizing the N-terminal carbamate and the aromatic substituent on the (4R)-hydroxyproline moiety. Inhibitors meeting the potency criteria in the cell-based assay and with improved oral bioavailability in rats were identified. **BILN ***2061*** was selected as the best compound, the first NS3 protease inhibitor reported with antiviral activity in man.

SUPPL. TERM: antiviral design hepatitis C virus NS3 protease BILN2061 structure; macrocyclic tripeptide prepn HCV NS3 protease inhibitor antiviral structure

INDEX TERM: Structure-activity relationship
(HCV protease-inhibiting; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: Tripeptides
ROLE: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(macrocyclic; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: Antiviral agents
Drug bioavailability
Drug design
Human
Peptidomimetics
(structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: Macrocyclic compounds
ROLE: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: **300832-84-2P**
ROLE: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(**BILN 2061**; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 9001-92-7P, Protease
ROLE: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(HCV NS3 protease; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 463-77-4, Carbamic acid, properties
ROLE: PRP (Properties)
(N-terminal; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 51-35-4, Hydroxyproline
ROLE: PRP (Properties)
(moiety; structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 300832-73-9P
ROLE: PAC (Pharmacological activity); PKT

(Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 300831-82-7P 300831-83-8P 300832-25-1P 300832-37-5P
300832-38-6P 300832-40-0P 300832-44-4P 300832-51-3P
300832-53-5P 300832-55-7P 300832-56-8P 300832-60-4P
300832-64-8P 300832-66-0P 300832-67-1P 300832-71-7P
300832-72-8P 300832-74-0P 300832-83-1P 300832-85-3P
579472-70-1P 652160-88-8P 652160-90-2P
ROLE: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

INDEX TERM: 82121-05-9D, 4-Hydroxy-7-methoxyquinoline, 2-substituted derivs.
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN 2061**)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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Choo, Q	1989	244	359	Science	HCAPLUS
Cornberg, M	2002	4	23	Curr Gastroenterol R	
Denissen, J	1995	23	185	Drug Metab Dispos	
Goudreau, N	2004	47	123	J Med Chem	HCAPLUS
Greene, T	1999		518	Protective Groups in	
Hagedorn, C	2000	242		Curr Top Microbiol I	HCAPLUS
Hepatitis, C	1996	71	346	Wkly Epidemiol Rec	
Kolykhalov, A	2000	74	2046	J Virol	HCAPLUS
Lamarre, D	2003	426	186	Nature	HCAPLUS
Laplante, S	2000	10	2271	Bioorg Med Chem Lett	HCAPLUS
Laplante, S	1999	274	18618	J Biol Chem	HCAPLUS
Lesk, A	1996	258	501	J Mol Biol	HCAPLUS
Lipinski, C	1997	1-3	3	Adv Drug Delivery Re	
Llinas-Brunet, M	1998	8	1713	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	1998	8	2719	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2000	10	2267	Bioorg Med Chem Lett	HCAPLUS
Pause, A	2003	278	20374	J Biol Chem	HCAPLUS
Poupart, M	2001	66	4743	J Org Chem	HCAPLUS
Rancourt, J				J Med Chem, in press	
Reed, K	2000	242	55	Curr Top Microbiol I	HCAPLUS
Steinkuhler, C	1998	37	8899	Biochemistry	MEDLINE
Steinkuhler, C	2001	8	919	Curr Med Chem	HCAPLUS
Tsantrizos, Y	2003			US 6608027 B1	HCAPLUS
Tsantrizos, Y	2003	42	1356	Angew Chem, Int Ed	HCAPLUS
Tsantrizos, Y				Manuscript in prepar	
Yoakim, C	2003		473	Synlett	HCAPLUS

L41 ANSWER 7 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:392478 HCAPLUS
DOCUMENT NUMBER: 140:400031
ENTRY DATE: Entered STN: 14 May 2004
TITLE: Macrocyclic compound-containing compositions for the treatment of infection by Flaviviridae viruses
INVENTOR(S): Lamarre, Daniel; Lagace, Lisette
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: C07K005-08
SECONDARY: A61K038-05; A61K038-06; A61P031-14
CLASSIFICATION: 1-5 (Pharmacology)
Section cross-reference(s): 34, 63
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004039833	A1	20040513	WO 2003-CA1634	20031024

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ,
BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-421900P P 20021029
US 2003-442769P P 20030127

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004039833	ICM	C07K005-08
	ICS	A61K038-05; A61K038-06; A61P031-14

OTHER SOURCE(S): MARPAT 140:400031

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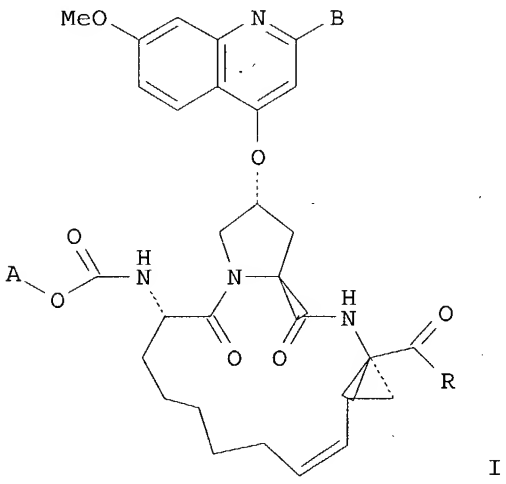

I

ABSTRACT:
The invention relates to macrocyclic compds. I [A is alkyl or cycloalkyl; B is Ph or thiazolyl, which may be substituted by alkylamino or alkanoylamino; R is OH or NHSO2R2, where R2 is (un)substituted alkyl, cycloalkyl or aryl] or their pharmaceutically-acceptable salts for the treatment of a mammal infected with a virus of the Flaviviridae family. Thus, IC50 values for compound I [A is cyclopentyl, B is 2-(isopropylamino)-4-thiazolyl, R is OH] against HCV NS3-NS4A protease are shown graphically.

SUPPL. TERM: macrocyclic peptide treatment Flaviviridae virus; hepatitis C virus protease inhibitor macrocyclic peptide

INDEX TERM: Peptides, biological studies
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic; macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

INDEX TERM: Antiviral agents
Flaviviridae
Hepatitis C virus

Hepatitis GB virus B
(macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

INDEX TERM: Macrocyclic compounds
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

INDEX TERM: Infection
(viral; macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

INDEX TERM: 149885-80-3
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

INDEX TERM: 300831-83-8 300832-25-1 **300832-84-2**
552335-24-7 681145-23-3 681145-24-4
ROLE: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

INDEX TERM: 688867-90-5 688867-91-6 688867-95-0 688867-96-1
688867-98-3 688867-99-4 688868-00-0 688868-01-1
688868-02-2 688868-03-3
ROLE: PRP (Properties)
(unclaimed nucleotide sequence; macrocyclic compound-containing
compns. for the treatment of infection by Flaviviridae viruses)

INDEX TERM: 688867-92-7 688867-93-8 688867-94-9 688867-97-2
ROLE: PRP (Properties)
(unclaimed protein sequence; macrocyclic compound-containing compns. for the treatment of infection by Flaviviridae viruses)

INDEX TERM: 259221-97-1 688747-48-0 688868-04-4 688868-05-5
688868-06-6 688868-07-7 688868-08-8 688868-09-9
688868-10-2 688868-11-3 688868-12-4 688868-13-5
ROLE: PRP (Properties)
(unclaimed sequence; macrocyclic compound-containing compns. for the treatment of infection by Flaviviridae viruses)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Boehringer Ingelheim Ca	2000			WO 0059929 A	HCAPLUS

Boehringer Ingelheim Ph	2003			WO 03066103 A	HCAPLUS
Buchen-Osmond, C	2003		1	www.ncbi.nlm.nih.gov	
Buchen-Osmond, C	2003		1	www.ncbi.nlm.nih.gov	
Buchen-Osmond, C	2003		1	www.ncbi.nlm.nih.gov	
Buchen-Osmond, C	2003		1	www.ncbi.nlm.nih.gov	
Llinas-Brunet, M	2003			WO 03064455 A	HCAPLUS
Squibb Bristol Myers Co	2003			WO 03053349 A	HCAPLUS

L41 ANSWER 8 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:370958 HCAPLUS
DOCUMENT NUMBER: 140:357673
ENTRY DATE: Entered STN: 07 May 2004
TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus
INVENTOR(S): Llinas-Brunet, Montse; Bailey, Murray D.
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.h., Germany
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: C07K005-08
SECONDARY: A61K038-06
CLASSIFICATION: 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037855	A1	20040506	WO 2003-CA1604	20031020

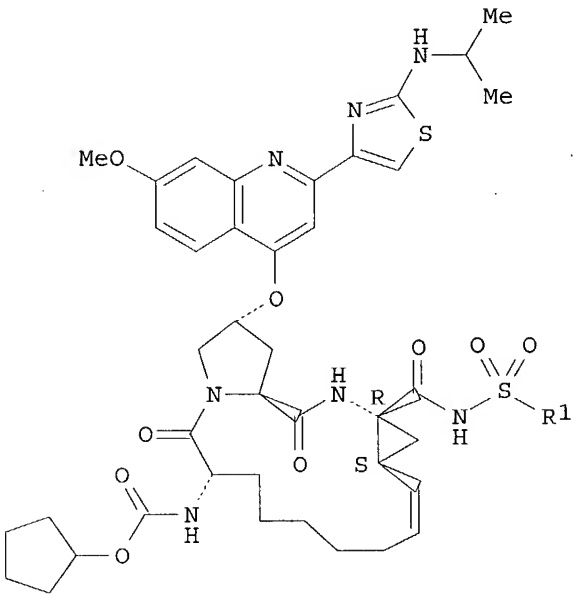
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 2002-421414P P 20021025
US 2002-433820P P 20021216
US 2003-442768P P 20030127

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004037855	ICM	C07K005-08
	ICS	A61K038-06

OTHER SOURCE(S): MARPAT 140:357673
GRAPHIC IMAGE:



I

ABSTRACT:
Macrocyclic peptides I [R1 is (un)substituted alkyl, cycloalkyl, alkylcycloalkyl, aryl or heteroaryl] or their pharmaceutically-acceptable salts were prepared as inhibitors of the hepatitis C virus (HCV) NS3 protease. Thus, I (R = Me) was prepared by a multistep sequence involving peptide coupling, olefin metathesis to form the macrocycle and methanesulfonamidation.

SUPPL. TERM:	macrocyclic peptide prepn inhibitor hepatitis C virus protease
INDEX TERM:	Peptides, preparation ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (cyclic; preparation of macrocyclic peptides active against the hepatitis C virus)
INDEX TERM:	Hepatitis C virus (preparation of macrocyclic peptides active against the hepatitis C virus)
INDEX TERM:	Interferons ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (α, pharmaceutical agents; preparation of macrocyclic peptides active against the hepatitis C virus)
INDEX TERM:	36791-04-5, Ribavirin ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (pharmaceutical agent; preparation of macrocyclic peptides active against the hepatitis C virus)
INDEX TERM:	149885-80-3, NS3 protease ROLE: BSU (Biological study, unclassified); BIOL (Biological study) (preparation of macrocyclic peptides active against the hepatitis C virus)
INDEX TERM:	552335-24-7P 681145-23-3P 681145-24-4P 681145-25-5P 681145-26-6P 681145-27-7P 681145-28-8P 681145-29-9P

681145-30-2P 681145-32-4P 681145-33-5P 681145-34-6P
681145-35-7P 681145-36-8P 681145-37-9P 681145-38-0P
681145-39-1P 681145-40-4P 681145-41-5P 681145-42-6P
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 96-41-3, Cyclopentanol 98-10-2, Benzenesulfonamide 1068-90-2, Diethyl acetamidomalonate 1719-76-2, Isopropylthiourea 3144-09-0, Methanesulfonamide 13726-69-7 85866-02-0, 7 Octene 1 2 diol 154350-29-5, Cyclopropanesulfonamide 259214-73-8 681260-04-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 17206-61-0P, 6 Heptenal 54681-67-3P 300831-19-0P 300831-20-3P 300831-21-4P 300831-45-2P 300831-46-3P 300831-72-5P 300831-74-7P 300831-75-8P 300831-76-9P 300831-77-0P **300832-84-2P** 572922-89-5P 572922-90-8P 572922-91-9P 681145-21-1P 681145-22-2P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of macrocyclic peptides active against the hepatitis C virus)

L41 ANSWER 9 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:590266 HCAPLUS
DOCUMENT NUMBER: 141:184653
ENTRY DATE: Entered STN: 25 Jul 2004
TITLE: Sensitivity of NS3 serine proteases from hepatitis C virus genotypes 2 and 3 to the inhibitor **BILN 2061**
AUTHOR(S): Thibeault, Diane; Bousquet, Christiane; Gingras, Rock; Lagace, Lisette; Maurice, Roger; White, Peter W.; Lamarre, Daniel
CORPORATE SOURCE: Department of Biological Sciences, Research and Development, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Journal of Virology (2004), 78(14), 7352-7359
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-5 (Pharmacology)
Section cross-reference(s): 3, 7, 10

ABSTRACT:
Hepatitis C virus (HCV) displays a high degree of genetic variability. Six genotypes and more than 50 subtypes have been identified to date. In this report, kinetic profiles were determined for NS3 proteases of genotypes 1a, 1b, 2ac, 2b, and 3a, revealing no major differences in activity. In vitro sensitivity studies with **BILN 2061** showed a decrease in affinity for proteases of genotypes 2 and 3 (Ki, 80 to 90 nM) compared to genotype 1 enzymes (Ki, 1.5 nM). To understand the reduced sensitivity of genotypes 2 and 3 to ***BILN*** **2061**, active-site residues in the proximity of the inhibitor binding site were replaced in the genotype-1b enzyme with the corresponding genotype-2b or -3a residues. The replacement of five residues at positions 78, 79, 80, 122, and 132 accounted for most of the reduced sensitivity of genotype 2b, while replacement of residue 168 alone could account for the reduced sensitivity of genotype 3a. **BILN**

2061 remains a potent inhibitor of these non-genotype-1 NS3-NS4A proteins, with Ki values below 100 nM. This in vitro potency, in conjunction with the good pharmacokinetic data reported for humans, suggests that there is potential for **BILN 2061** as an antiviral agent for individuals infected with non-genotype-1 HCV.

SUPPL. TERM: hepatitis C virus NS3 serine protease variant BILN2061 antiviral; enzyme active site mutation NS3NS4A heterodimer BILN2061 affinity genotype

INDEX TERM: Hepatitis
(C; HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: Antiviral agents
Genotypes
Hepatitis C virus
Human
Mutation
(HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: Proteins
ROLE: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(NS3-NS4A heterodimer; HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: Enzyme functional sites
(active; HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: Drug resistance
(antiviral; HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: Molecular association
(effect of HCV NS3-NS4A genotype variation on NS3 protease on BILN 2061affinity; HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: Enzyme kinetics
(of inhibition, of NS3-NS4A heterodimer protein of genotypes 1, 2, and 3; HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: Antiviral agents
(resistance to; HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: 149885-80-3, NS3 serine protease
ROLE: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor **BILN 2061**)

INDEX TERM: **300832-84-2, BILN 2061**
ROLE: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor **BILN 2061**)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Beyer, B	2001	43	82	Proteins	HCAPLUS
Bianchi, E	1996	237	239	Anal Biochem	HCAPLUS
Bodansky, M	1993			Peptide chemistry, 2	
Di Bisceglie, A	2002	36	S121	Hepatology	
Domingo, E	2002	82	39	Virus Res	HCAPLUS
Drake, J	1999	96	13910	Proc Natl Acad Sci U	HCAPLUS
Hoofnagle, J	2002	36	S21	Hepatology	
Kakiuchi, N	1995	210	1059	Biochem Biophys Res	HCAPLUS
Kim, J	1996	87	343	Cell	HCAPLUS
Koch, U	2001	40	631	Biochemistry	HCAPLUS
Kolykhalov, A	2000	74	2046	J Virol	HCAPLUS
Lamarre, D	2003	426	186	Nature	HCAPLUS
Laplante, S	1999	274	18618	J Biol Chem	HCAPLUS
Lin, C	1995	69	4373	J Virol	HCAPLUS
Llinas-Brunet, M	1998	8	1713	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	1998	8	2719	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2000	10	2267	Bioorg Med Chem Lett	HCAPLUS
Mondelli, M	1999	31	65	J Hepatol	

Muzammil, S	2003	42	631	Biochemistry	HCAPLUS
Neumann, A	1998	282	103	Science	HCAPLUS
Pause, A	2003	278	20374	J Biol Chem	HCAPLUS
Pawlotsky, J	2003	7	45	Clin Liver Dis	
Reed, K	2000	242	55	Curr Top Microbiol I	HCAPLUS
Simmonds, P	2001	82	693	J Gen Virol	HCAPLUS
Simmonds, P	1999	31	54	J Hepatol	
Steinhuhler, C	2001	8	919	Curr Med Chem	
Taliani, M	1996	240	60	Anal Biochem	HCAPLUS
Trozzi, C	2003	77	3669	J Virol	HCAPLUS
Tsantrizos, Y	2003			US 6608027 B1	HCAPLUS
Tsantrizos, Y	2003	42	1355	Angew Chem Int Ed	
Webster, G	2000	14	229	Bailliere's Clin Gas	MEDLINE
Wright-Minogue, J	2000	32	497	J Hepatol	HCAPLUS
Yan, Y	1998	7	837	Protein Sci	HCAPLUS

L41 ANSWER 10 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:580783 HCAPLUS
DOCUMENT NUMBER: 141:261053
ENTRY DATE: Entered STN: 21 Jul 2004
TITLE: Synthesis of **BILN 2061**, an HCV NS3 Protease Inhibitor with Proven Antiviral Effect in Humans
AUTHOR(S): Faucher, Anne-Marie; Bailey, Murray D.; Beaulieu, Pierre L.; Brochu, Christian; Duceppe, Jean-Simon; Ferland, Jean-Marie; Ghiro, Elise; Gorys, Vida; Halmos, Ted; Kawai, Stephen H.; Poirier, Martin; Simoneau, Bruno; Tsantrizos, Youla S.; Llinas-Brunet, Montse
CORPORATE SOURCE: Chemistry Department, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Organic Letters (2004), 6(17), 2901-2904
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

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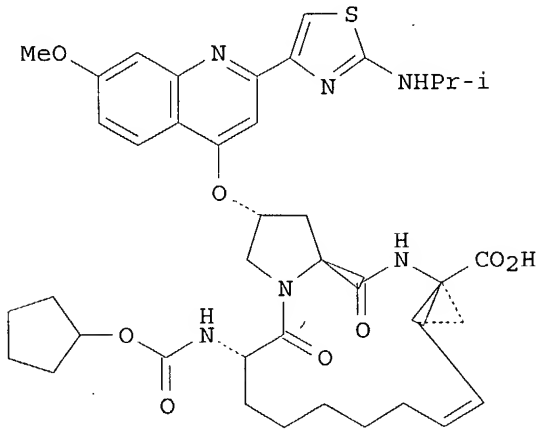

I

ABSTRACT:
The synthesis of **BILN 2061** (I), a hepatitis C virus (HCV) NS3 protease inhibitor with proven antiviral effect in humans, was accomplished in a convergent manner from four building blocks. The procedure described here was suitable for the preparation of multigram quantities of **BILN** ***2061*** for preclin. pharmacol. evaluation.

SUPPL. TERM: **BILN 2061** peptide macrocycle prepn
antiviral agent human

INDEX TERM: Substitution reaction, nucleophilic
(Mitsunobu; total synthesis of peptidyl macrocycle **BILN-2061**)

INDEX TERM: Cyclization
(metathesis; total synthesis of peptidyl macrocycle **BILN-2061**)

INDEX TERM: Antiviral agents
Hepatitis C virus
Human
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: Macrocyclic compounds
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: Metathesis
(ring-closing; total synthesis of peptidyl macrocycle **BILN-2061**)

INDEX TERM: Hydrogenation
(stereoselective; total synthesis of peptidyl macrocycle **BILN-2061**)

INDEX TERM: Asymmetric synthesis and induction
(total synthesis of peptidyl macrocycle **BILN-2061**)

INDEX TERM: Infection
(viral; preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: 149885-80-3, NS3 protease
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: 142184-30-3, [(COD)Rh(S,S)-Et-DuPHOS)]OTF 203714-71-0
ROLE: CAT (Catalyst use); USES (Uses)
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: **300832-84-2P**
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: 1068-90-2 13726-69-7 50715-28-1 85866-02-0,

7-Octene-1,2-diol 259214-73-8 681260-04-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

INDEX TERM: 17206-61-0P, 6-Heptenal 54681-67-3P 300831-20-3P 300831-21-4P 300831-45-2P 300831-46-3P 300831-72-5P 300831-74-7P 572922-89-5P 572922-91-9P 681145-22-2P 756894-33-4P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptidyl macrocycle **BILN-2061**, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Bailey, M	2004			J Med Chem	
Beaulieu, P	2002	1	163	Curr Med Chem:Anti-I	HCAPLUS
Benhamou, Y	2002	36	304A	Hepatology, Abst 563	
Burk, M	1998	120	657	J Am Chem Soc	HCAPLUS
Burk, M	1997	62	7054	J Org Chem	HCAPLUS
Choo, Q	1989	244	359	Science	HCAPLUS
Cornberg, M	2002	4	23	Curr Gastroenterol R	
Furstner, A	2000	39	3012	Angew Chem, Int Ed	HCAPLUS
Goudreau, N	2004	47	123	J Med Chem	HCAPLUS
Hagedorn, C	2000	242		Curr Top Microbiol I	HCAPLUS
Hengartner, U	1979	44	3741	J Org Chem	HCAPLUS
Hinrichsen, H	2002	36	297A	Hepatology, Abst 866	
Huang, J	1999	121	2674	J Am Chem Soc	HCAPLUS
Johnson, J	1942	1	210	Organic Reactions, C	
Kingsbury, J	1999	121	791	J Am Chem Soc	HCAPLUS
Knorr, R	1989	30	1927	Tetrahedron Lett	HCAPLUS
Kolykalov, A	2000	74	2046	J Virol	
Lamarre, D	2003	426	186	Nature	HCAPLUS
Laplante, S	2000	10	2271	Bioorg Med Chem Lett	HCAPLUS
Liu, K	1979	31	80	Taiwan Yaoxue Zazhi	HCAPLUS
Llinas-Brunet, M	2000			US 6323180 B1	HCAPLUS
Llinas-Brunet, M	1998	8	1713	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2000	10	2267	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2004	47	1605	J Med Chem	HCAPLUS
Miller, S	1996	118	9606	J Am Chem Soc	HCAPLUS
Mitsunobu, O	1981		1	Synthesis	HCAPLUS
Pham, T	1994	59	3676	J Org Chem	HCAPLUS
Poirier, M				Manuscript in prepar	
Poupart, M	2001	66	4743	J Org Chem	HCAPLUS
Rancourt, J	2004	47	2511	J Med Chem	HCAPLUS
Reed, K	2000	242	55	Curr Top Microbiol I	HCAPLUS
Reiser, M	2003	38	221A	Hepatology	
Schechter, I	1967	27	157	Biochem Biophys Res	HCAPLUS
Scholl, M	1999	40	2247	Tetrahedron Lett	HCAPLUS
Schrock, R	2003	42	4592	Angew Chem, Int Ed	HCAPLUS
Steinkuler, C	1998	37	8899	Biochemistry	
Trnka, T	2001	34	18	Acc Chem Res	HCAPLUS
Tsantrisos, Y	2003			US 6608027	HCAPLUS
Tsantrizos, Y	2003	42	1355	Angew Chem, Int Ed	

L41 ANSWER 11 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:561437 HCAPLUS
ENTRY DATE: Entered STN: 14 Jul 2004
TITLE: **BILN 2061**: a major step toward new therapeutic strategies in hepatitis C
AUTHOR(S): Asselah, Tarik; Marcellin, Patrick
CORPORATE SOURCE: Service d'Hepatologie, INSERM U 481, Centre de Recherche Claude Bernard sur les Hepatites Virales, Clichy, 92110, Fr.
SOURCE: Journal of Hepatology (2004), 41(1), 178-181
CODEN: JOHEEC; ISSN: 0168-8278
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

CLASSIFICATION: 1 (Pharmacology)
ABSTRACT: Unavailable
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S):
(1) Anon; Hepatology 2002, V36
(2) Anon; J Hepatol 1999, V31, P1
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(12) Lohmann, V; Science 1999, V285, P110 HCAPLUS
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(14) Marcellin, P; Hepatology 2002, V36, PS47
(15) Narjes, H; Hepatology 2002, V36, P800
(16) Pause, A; J Biol Chem 2003, V278, P20374 HCAPLUS
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(18) Steinkuhler, C; Biochemistry 1998, V37, P8899 MEDLINE
(19) Trozzi, C; J Virol 2003, V77, P3669 HCAPLUS

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	2002	36		Hepatology	
Anon	1999	31	1	J Hepatol	
Benhamou, Y	2002	36		Hepatology	
Blight, K	2000	290	1972	Science	HCAPLUS
Dhumeaux, D	2003	52	1784	Gut	MEDLINE
Foy, E	2003	300	1145	Science	HCAPLUS
Hinrichsen, H	2002	36		Hepatology	
Kato, T	2003	125	1808	Gastroenterology	HCAPLUS
Kim, J	1996	87	343	Cell	HCAPLUS
Lamarre, D	2003	426	186	Nature	HCAPLUS
Lin, C	2004	279	17508	J Biol Chem	HCAPLUS
Lohmann, V	1999	285	110	Science	HCAPLUS
Love, R	1996	87	331	Cell	HCAPLUS
Marcellin, P	2002	36	S47	Hepatology	
Narjes, H	2002	36	800	Hepatology	
Pause, A	2003	278	20374	J Biol Chem	HCAPLUS
Reiser, M	2003	38		Hepatology	
Steinkuhler, C	1998	37	8899	Biochemistry	MEDLINE
Trozzi, C	2003	77	3669	J Virol	HCAPLUS

L41 ANSWER 12 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:633516 HCAPLUS
DOCUMENT NUMBER: 139:185670
ENTRY DATE: Entered STN: 15 Aug 2003
TITLE: Pharmaceutical compositions for hepatitis C viral protease inhibitors
INVENTOR(S): Chen, Shirlynn; Mei, Xiaohui
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:

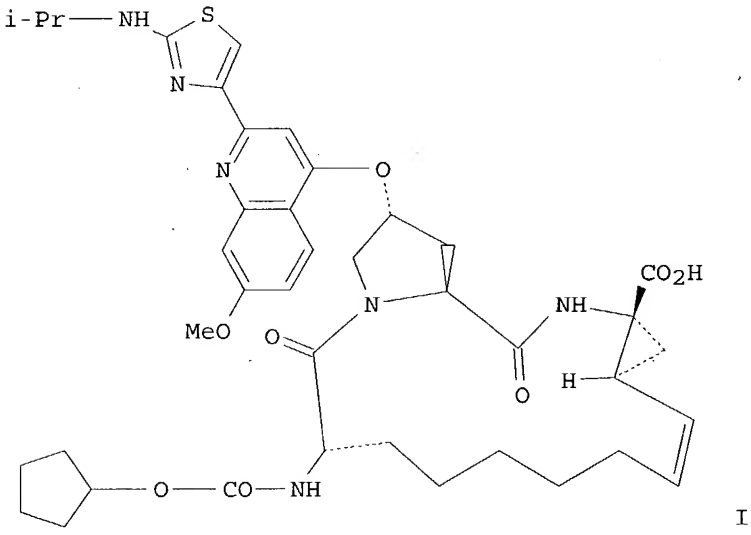
MAIN: A61K047-18
SECONDARY: A61K038-05; A61K038-06
CLASSIFICATION: 63-6 (Pharmaceuticals)
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003066103	A1	20030814	WO 2003-US3380	20030205
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003195228	A1	20031016	US 2003-357919	20030204

PRIORITY APPLN. INFO.: US 2002-355694P P 20020207
PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003066103	ICM	A61K047-18
	ICS	A61K038-05; A61K038-06

OTHER SOURCE(S): MARPAT 139:185670
GRAPHIC IMAGE:



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ABSTRACT:
Disclosed are pharmaceutical compns. of hepatitis C viral protease inhibitors having improved bioavailability, and methods of using these compns. for inhibiting the replication of the hepatitis C virus (HCV) and for the treatment of an HCV infection. These compns. include co-solvent systems, lipid based

systems, solid dispersions and granulations, and all comprise the hepatitis C viral protease inhibitor, at least one pharmaceutically acceptable amine and optionally one or more addnl. ingredients. A composition contained I 4, tromethamine 3.2, water 44.8, ethanol 21.3, and propylene glycol 26.7 weight/weight%.

SUPPL. TERM: hepatitis C viral protease inhibitor pharmaceutical
INDEX TERM: Drug delivery systems
(capsules; pharmaceutical compns. for hepatitis C viral protease inhibitors)
INDEX TERM: Castor oil
ROLE: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethoxylated; pharmaceutical compns. for hepatitis C viral protease inhibitors)
INDEX TERM: Antioxidants
Drug bioavailability
(pharmaceutical compns. for hepatitis C viral protease inhibitors)
INDEX TERM: Polyoxyalkylenes, biological studies
ROLE: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. for hepatitis C viral protease inhibitors)
INDEX TERM: Drug delivery systems
(powders; pharmaceutical compns. for hepatitis C viral protease inhibitors)
INDEX TERM: Drug delivery systems
(tablets; pharmaceutical compns. for hepatitis C viral protease inhibitors)
INDEX TERM: 9001-92-7, Protease
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(hepatitis C virus; pharmaceutical compns. for hepatitis C viral protease inhibitors)
INDEX TERM: 300832-84-2
ROLE: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. for hepatitis C viral protease inhibitors)
INDEX TERM: 57-55-6, Propylene glycol, biological studies 64-17-5, Ethanol, biological studies 77-86-1, Tris 151-21-3, Sodium lauryl sulfate, biological studies 7732-18-5, Water, biological studies 9002-96-4, α-Tocopheryl polyethylene glycol succinate 9003-39-8, Pvp 25322-68-3, Peg 106392-12-5, Oxirane, polymer with methyloxirane, block
ROLE: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. for hepatitis C viral protease inhibitors)
INDEX TERM: 300832-64-8 300832-66-0 300832-67-1 300832-69-3
300832-70-6 300832-71-7 300832-72-8 300832-73-9
300832-74-0 300832-76-2 300832-77-3 300832-78-4
300832-79-5 300832-80-8 300832-81-9 300832-83-1
300832-85-3 300832-86-4 572922-86-2 572922-94-2
577965-78-7 577965-82-3 577965-83-4
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. for hepatitis C viral protease

inhibitors)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD.
REFERENCE(S): (1) Boehringer Ingelheim Ca Ltd; WO 0059929 A 2000 HCAPLUS
(2) Morozowich, W; WO 9906044 A 1999 HCAPLUS

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Boehringer Ingelheim Ca	2000			WO 0059929 A	HCAPLUS
Morozowich, W	1999			WO 9906044 A	HCAPLUS

L41 ANSWER 13 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:511084 HCAPLUS
DOCUMENT NUMBER: 139:69527
ENTRY DATE: Entered STN: 04 Jul 2003
TITLE: Preparation of macrocyclic compounds as inhibitors of hepatitis C virus
INVENTOR(S): Campbell, Jeffrey Allen; Good, Andrew Charles
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 225 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K
CLASSIFICATION: 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 63
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003053349	A2	20030703	WO 2002-US39926	20021213
WO 2003053349	A3	20040115		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004038872	A1	20040226	US 2002-317451	20021212
EP 1455809	A2	20040915	EP 2002-795860	20021213
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.:

US 2001-344080P	P	20011220
US 2002-382103P	P	20020520
WO 2002-US39926	W	20021213

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003053349	ICM	A61K

OTHER SOURCE(S): MARPAT 139:69527
GRAPHIC IMAGE:

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

ABSTRACT:
The invention relates to macrocyclic compds. I [R1 = (cyclo)alkyl; R2 = H, halo, alkyl, alkoxy, cycloalkoxy, (un)substituted aryl or heterocyclyl; R3 = H, halo, CF3, alkoxy, cycloalkoxy; R4 = NH2 or NHR6, where R6 is alkanoyl, alkylaminocarbonyl, or carbalkoxy; Q is a 3-9 atom (un)saturated alkylene chain optionally containing 1-3 heteroatoms O, S, SO, or SO2], including methods for their synthesis and use in pharmaceutical compns. for therapeutic or prophylactic prevention or treatment of hepatitis C virus (HCV) infection. Thus, 3,13-diazatricyclo[11.3.0.04,6]hexadec-7-ene derivative II was prepared by a multistep procedure and assayed for inhibition of HCV NS3/4A protease (IC50 < 5 μM).

SUPPL. TERM: macrocyclic peptide prepn inhibitor hepatitis C virus

INDEX TERM: Peptides, preparation
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: Antiviral agents
Hepatitis C virus
Human
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: Macrocyclic compounds
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: Infection
(viral; preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 552334-90-4P 552334-92-6P 552334-94-8P 552334-96-0P 552334-98-2P 552334-99-3P
ROLE: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 552334-91-5P 552334-93-7P 552334-95-9P 552334-97-1P
ROLE: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 259214-55-6P 259217-95-3P
ROLE: BPN (Biosynthetic preparation); RCT (Reactant); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 300831-62-3P 300831-63-4P 300831-83-8P 445305-87-3P

445305-88-4P 445305-89-5P 552335-25-8P 552335-26-9P
552335-27-0P 552335-28-1P 552335-29-2P 552335-30-5P
552335-31-6P 552335-32-7P 552335-33-8P 552335-34-9P
552335-35-0P
ROLE: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 9004-06-2, Elastase 9004-07-3, Chymotrypsin 9047-22-7, Cathepsin b 149885-80-3, Ns3 protease
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 213316-49-5P
ROLE: CPS (Chemical process); PEP (Physical, engineering or chemical process); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 552335-03-2P 552335-04-3P 552335-05-4P 552335-21-4P
ROLE: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 552335-00-9P 552335-01-0P 552335-02-1P 552335-06-5P
552335-07-6P 552335-08-7P 552335-09-8P 552335-10-1P
552335-12-3P 552335-13-4P 552335-14-5P 552335-15-6P
552335-16-7P 552335-17-8P 552335-18-9P 552335-19-0P
552335-20-3P 552335-22-5P 552335-23-6P 552335-24-7P
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 94-02-0, Ethyl benzoylacetate 100-52-7, Benzaldehyde, reactions 462-27-1, 2 Fluoroethyl chloroformate 536-90-3, m-Anisidine 563-80-4, 3 Methyl 2 butanone 611-35-8, 4 Chloroquinoline 623-33-6, Glycine ethyl ester hydrochloride 821-06-7, trans-1 4 Dibromo 2 butene 1119-51-3, 1 Bromo 4 pentene 1609-86-5, tert-Butyl isocyanate 1719-76-2, Isopropylthiourea 2033-24-1, Meldrum's acid 3144-09-0, Methanesulfonamide 4399-47-7, Cyclobutyl bromide 4910-62-7, Diazenedicarboxylic acid dipotassium salt 5239-82-7, Cyclopropylacetic acid 13726-69-7 16982-21-1 20412-38-8, Neopentyl chloroformate 23779-97-7 40216-83-9 50715-28-1, Cyclopentyl chloroformate 55757-46-5 69555-14-2 89641-80-5 102195-79-9 139631-62-2, Cyclopropanesulfonyl chloride 178153-11-2 204711-97-7 208522-13-8 259214-75-0 300831-21-4 552335-71-4 552335-72-5
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 19967-55-6P, 1 Bromo 3 methyl 2 butanone 40682-54-0P 42465-53-2P 82121-05-9P 154350-29-5P,

Cyclopropanesulfonamide 156589-82-1P 189816-04-4P
189816-05-5P 213699-52-6P 259214-37-4P 259214-54-5P
259214-56-7P 259214-64-7P 300830-83-5P 300831-06-5P
300831-07-6P 300831-08-7P 300831-33-8P 300831-81-6P
300831-89-4P 300832-25-1P 300832-47-7P
300832-84-2P 445305-91-9P, Cyclobutanesulfonamide
552335-36-1P 552335-37-2P 552335-39-4P 552335-40-7P
552335-41-8P 552335-42-9P 552335-43-0P 552335-44-1P
552335-45-2P 552335-46-3P 552335-47-4P 552335-48-5P
552335-49-6P 552335-50-9P 552335-51-0P 552335-52-1P
552335-53-2P 552335-54-3P 552335-55-4P 552335-56-5P
552335-57-6P 552335-58-7P 552335-59-8P 552335-60-1P
552335-61-2P 552335-62-3P 552335-63-4P 552335-64-5P
552335-65-6P 552335-66-7P 552335-67-8P 552335-68-9P
552335-69-0P 552335-70-3P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

INDEX TERM: 552335-38-3P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)

L41 ANSWER 14 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:648255 HCAPLUS
DOCUMENT NUMBER: 139:197768
ENTRY DATE: Entered STN: 20 Aug 2003
TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus
INVENTOR(S): Tsantrizos, Youla S.; Cameron, Dale R.; Faucher, Anne-Marie; Ghiro, Elise; Goudreau, Nathalie; Halmos, Teddy; Llinas-Brunet, Montse
PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.
SOURCE: U.S., 90 pp., Cont.-in-part of U.S. Ser. No. 542,675, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K038-05
SECONDARY: A61K038-06; A61K038-12; C07K005-08; C07K005-12
US PATENT CLASSIF.: 514009000; 514010000; 514011000; 514018000; 514019000; 530317000; 530321000; 530331000; 540454000; 540455000
CLASSIFICATION: 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 15
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

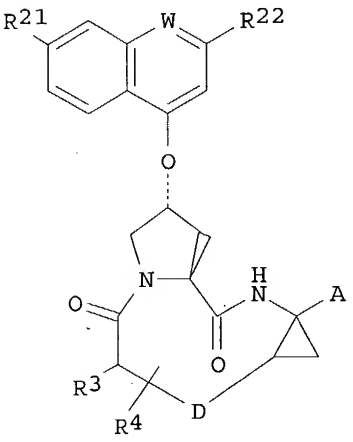
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6608027	B1	20030819	US 2001-760946	20010116
EP 1437362	A1	20040714	EP 2004-9264	20000403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
US 2004002448	A1	20040101	US 2003-358726	20030205
PRIORITY APPLN. INFO.:			US 1999-128011P	P 19990406
			US 2000-542675	B2 20000403
			EP 2000-913999	A3 20000403
			US 2001-760946	A1 20010116

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6608027	ICM	A61K038-05
	ICS	A61K038-06; A61K038-12; C07K005-08; C07K005-12
	NCL	514009000; 514010000; 514011000; 514018000; 514019000; 530317000; 530321000; 530331000; 540454000; 540455000
US 6608027	ECLA	C07K005/06H2; C07K005/08A
US 2004002448	ECLA	C07K005/06H2; C07K005/08A

OTHER SOURCE(S): MARPAT 139:197768

GRAPHIC IMAGE:



I

ABSTRACT:
Macrocyclic peptides I [W = CH or N; R21 = H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy, or an amino group; R22 = H, halo, alkyl, cycloalkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkyl, aryl or heteroaryl; R3 = hydroxy, NH2, aryl- or heteroarylamino, NHCOR32, CONHR32, CO2R32, where R32 is alkyl or cycloalkyl; D is a 5 to 10-atom saturated or unsatd. alkylene chain optionally containing one to three heteroatoms independently selected from: O, S, or NH or substituted imino; R4 = H or from one to three substituents at any carbon atom of chain D; A is an amide or carboxylic acid group or a pharmaceutically acceptable salt or ester; two diastereomers may exist at the cyclopropane moiety] were prepared which are active in-vitro and in cellular assays against the NS3 protease of the hepatitis C virus. Thus, macrocyclic peptide I [W = N; R21, R22, R4 = H; A = CO2H; R3CH-D = (S)-(Me3CO2CNH)CH(CH2)3CH:CH(CH2)2-E (syn to acid)] was prepared and showed IC50 > 0.1 μM in the full-length NS3-NS4A heterodimer protein fluorogenic assay.

SUPPL. TERM: cyclic peptide prepn hepatitis C virus inhibitor

INDEX TERM: Hepatitis C virus
Immunomodulators
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: Macrocyclic compounds
Peptides, preparation
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological

study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: Interferons
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 37259-58-8, Serine protease
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM:

300831-32-7P	300831-33-8P	300831-34-9P	300831-79-2P
300831-80-5P	300831-81-6P	300831-82-7P	300831-83-8P
300831-84-9P	300831-85-0P	300831-86-1P	300831-87-2P
300831-88-3P	300831-89-4P	300831-90-7P	300831-91-8P
300831-92-9P	300831-93-0P	300831-94-1P	300831-95-2P
300831-96-3P	300831-97-4P	300831-98-5P	300831-99-6P
300832-00-2P	300832-01-3P	300832-02-4P	300832-03-5P
300832-04-6P	300832-05-7P	300832-06-8P	300832-07-9P
300832-08-0P	300832-09-1P	300832-10-4P	300832-11-5P
300832-12-6P	300832-13-7P	300832-14-8P	300832-15-9P
300832-16-0P	300832-17-1P	300832-18-2P	300832-19-3P
300832-20-6P	300832-21-7P	300832-22-8P	300832-23-9P
300832-24-0P	300832-25-1P	300832-26-2P	300832-27-3P
300832-28-4P	300832-29-5P	300832-30-8P	300832-31-9P
300832-32-0P	300832-33-1P	300832-34-2P	300832-35-3P
300832-36-4P	300832-37-5P	300832-38-6P	300832-39-7P
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300832-60-4P	300832-61-5P	300832-62-6P	300832-63-7P
~~300832-64-8P~~	~~300832-65-9P~~	~~300832-66-0P~~	~~300832-67-1P~~
300832-68-2P	300832-69-3P	300832-70-6P	300832-71-7P
300832-72-8P	300832-73-9P	300832-74-0P	300832-75-1P
300832-76-2P	300832-77-3P	300832-78-4P	300832-79-5P
300832-80-8P	300832-81-9P	300832-82-0P	300832-83-1P
300832-84-2P	300832-85-3P	300832-86-4P	
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300832-99-9P	300833-00-5P	300833-01-6P	300833-02-7P
301188-00-1P	572922-86-2P	572922-94-2P	577965-82-3P
577965-83-4P			

ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 62-56-6, Thiourea, reactions 78-39-7, Triethyl orthoacetate 79-22-1, Methyl chloroformate 98-88-4, Benzoyl chloride 105-56-6, Ethyl cyanoacetate 288-13-1, Pyrazole 288-32-4, Imidazole, reactions 333-20-0, Potassium thiocyanate 536-90-3, m-Anisidine 541-16-2, Di-tert-butyl malonate 543-27-1, Isobutyl chloroformate 563-80-4, 3-Methyl-2-butanone 590-42-1, tert-Butyl isothiocyanate 591-08-2, n-Acetylthiourea 598-52-7,

n-Methylthiourea 625-53-6, n-Ethylthiourea 696-59-3, 2,5-Dimethoxytetrahydrofuran 765-30-0, Cyclopropylamine 822-36-6, 4-Methylimidazole 934-60-1, 6-Methylpicolinic acid 1003-03-8, Cyclopentylamine 1068-90-2, Diethyl acetamidomalonate 1113-41-3, L-Penicillamine 1113-59-3, 3-Bromopyruvic acid 1119-51-3, 4-Pentenyl bromide 1719-76-2, Isopropylthiourea 2385-77-5 2592-18-9 2695-48-9, 8-Bromo-1-octene 3282-30-2, Pivaloyl chloride 4285-48-7 7554-65-6, 4-MethylPyrazole 10387-40-3, Potassium thioacetate 13726-85-7 16982-21-1, Ethyl thiooxamate 22059-22-9, Acetamidoxime 29681-39-8 50413-30-4 50715-28-1 82121-05-9, 4-Hydroxy-7-methoxyquinoline 85866-02-0, 7-Octene-1,2-diol 90719-32-7 102195-79-9 113240-46-3, Malonic acid monoallyl ester 126690-67-3 204711-97-7 259214-64-7 259214-73-8 300831-45-2 300831-47-4 300831-50-9 300831-58-7 300831-62-3 300831-65-6 300831-67-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 616-47-7P, 1-Methylimidazole 3350-20-7P 17206-61-0P, 6-Heptenal 19967-55-6P 20485-43-2P 27191-09-9P, m-Anisidine hydrochloride 29082-92-6P 31642-67-8P, 8-Nonenoic acid 42465-53-2P 55327-87-2P, Acetamidomalonic acid 56541-14-1P, n-Cyclopropylthiourea 56541-16-3P 70498-31-6P 72086-72-7P 79479-07-5P 99071-95-1P 102936-57-2P 112380-21-9P 112380-22-0P 126125-54-0P 156589-82-1P 300830-79-9P 300830-80-2P 300830-81-3P 300830-82-4P 300830-83-5P 300830-84-6P 300830-85-7P 300830-86-8P 300830-87-9P 300830-88-0P 300830-89-1P 300830-90-4P 300830-91-5P 300830-92-6P 300830-93-7P 300830-94-8P 300830-95-9P 300830-96-0P 300830-97-1P 300830-98-2P 300830-99-3P 300831-00-9P 300831-01-0P 300831-02-1P 300831-03-2P 300831-04-3P 300831-05-4P 300831-06-5P 300831-07-6P 300831-08-7P 300831-09-8P 300831-10-1P 300831-12-3P 300831-13-4P 300831-14-5P 300831-15-6P 300831-16-7P 300831-17-8P 300831-18-9P 300831-19-0P 300831-20-3P 300831-21-4P 300831-22-5P 300831-23-6P 300831-24-7P 300831-26-9P 300831-27-0P 300831-28-1P 300831-29-2P 300831-30-5P 300831-31-6P 300831-35-0P 300831-36-1P 300831-37-2P 300831-38-3P 300831-39-4P 300831-40-7P 300831-41-8P 300831-42-9P 300831-43-0P 300831-44-1P 300831-46-3P 300831-48-5P 300831-49-6P 300831-51-0P 300831-52-1P 300831-53-2P 300831-54-3P 300831-55-4P 300831-56-5P 300831-57-6P 300831-59-8P 300831-60-1P 300831-61-2P 300831-63-4P 300831-64-5P 300831-66-7P 300831-68-9P 300831-69-0P 300831-70-3P 300831-71-4P 300831-72-5P 300831-73-6P 300831-74-7P 300831-75-8P 300831-76-9P 300831-77-0P 300831-78-1P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 300831-11-2P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 768-94-5, Amantadine 36791-04-5, Ribavirin 42613-29-6, Helicase 81669-70-7, Metalloprotease

ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 581980-39-4
ROLE: PRP (Properties)
(unclaimed protein sequence; preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 154485-12-8 242478-20-2 259221-97-1
ROLE: PRP (Properties)
(unclaimed sequence; preparation of macrocyclic peptides active against the hepatitis C virus)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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Wieland	1959	626	154	Ann	HCAPLUS

L41 ANSWER 15 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:184286 HCAPLUS
ENTRY DATE: Entered STN: 11 Mar 2003
TITLE: Discovery of **BILN 2061**: A small-molecule inhibitor of the hepatitis C virus serine protease
AUTHOR(S): Llinas-Brunet, Montse; Bailey, Murray; Bolger, Gordon; Cameron, Dale; Cartier, Mireille; Faucher, Anne-Marie; Goudreau, Nathalie; Kukolj, George; Lagace, Lisette; Pause, Amim; Rancourt, Jean; Thibeault, Diane; Tsantrizos, Youla; Lamarre, Daniel
CORPORATE SOURCE: Research and Development, Boehringer Ingelheim (Canada) Ltd, Laval (Quebec), QC, H7S 2G5, Can.
SOURCE: Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-320. American Chemical Society: Washington, D. C.
CODEN: 69DSA4
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
ABSTRACT:
The inadequate efficacy and tolerability of current therapies for the infectious liver disease caused by Hepatitis C Virus have warranted significant efforts in the development of new therapeutics. Optimization studies on peptide inhibitors based on N-terminal cleavage products led to the discovery of **BILN 2061**, a small, selective and potent inhibitor of the NS3 serine protease. A distinguishing feature of **BILN** ***2061*** is the presence of a C-terminal carboxylic acid functionality which provides exquisite selectivity with respect to other proteases. ***BILN*** **2061** showed low nanomolar inhibition of HCV RNA replication using the replicon cell model system. **BILN 2061** is orally bioavailable in various animal species. In view of the potent activity in vitro, good PK data in animal models and adequate pre-clin. safety profile, **BILN 2061** was selected for in-depth clin. evaluation in man as a novel antiviral compound for the treatment of HCV infection.

L41 ANSWER 16 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:886572 HCAPLUS
DOCUMENT NUMBER: 140:122161
ENTRY DATE: Entered STN: 12 Nov 2003
TITLE: An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus
AUTHOR(S): Lamarre, Daniel; Anderson, Paul C.; Bailey, Murray; Beaulieu, Pierre; Bolger, Gordon; Bonneau, Pierre; Boes, Michael; Cameron, Dale R.; Cartier, Mireille; Cordingley, Michael G.; Faucher, Anne-Marie; Goudreau, Nathalie; Kawai, Stephen H.; Kukolj, George; Lagace, Lisette; LaPlante, Steven R.; Narjes, Hans; Poupart, Marc-Andre; Rancourt, Jean; Sentjens, Roel E.; St. George, Roger; Simoneau, Bruno; Steinmann, Gerhard; Thibeault, Diane; Tsantrizos, Youla S.; Weldon, Steven M.; Yong, Chan-Loi; Llinas-Brunet, Montse
CORPORATE SOURCE: Departments of Biological Sciences, Boehringer Ingelheim (Canada) Ltd, Laval, QC, H7S 2G5, Can.

SOURCE: Nature (London, United Kingdom) (2003), 426(6963), 186-189
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-5 (Pharmacology)

ABSTRACT:
Hepatitis C virus (HCV) infection is a serious cause of chronic liver disease worldwide with more than 170 million infected individuals at risk of developing significant morbidity and mortality. Current interferon-based therapies are suboptimal especially in patients infected with HCV genotype 1, and they are poorly tolerated, highlighting the unmet medical need for new therapeutics. The HCV-encoded NS3 protease is essential for viral replication and has long been considered an attractive target for therapeutic intervention in HCV-infected patients. Here we identify a class of specific and potent NS3 protease inhibitors and report the evaluation of **BILN 2061**, a small mol. inhibitor biol. available through oral ingestion and the first of its class in human trials. Administration of **BILN 2061** to patients infected with HCV genotype 1 for 2 days resulted in an impressive reduction of HCV RNA plasma levels, and established proof-of-concept in humans for an HCV NS3 protease inhibitor. Our results further illustrate the potential of the viral-enzyme-targeted drug discovery approach for the development of new HCV therapeutics.

SUPPL. TERM: NS3 protease inhibitor BILN2061 antiviral hepatitis C virus
INDEX TERM: Antiviral agents
Hepatitis C virus
Human
(NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus)
INDEX TERM: Viral RNA
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus)
INDEX TERM: 149885-80-3, NS3 protease
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus)
INDEX TERM: **300832-84-2, BILN 2061**
ROLE: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD.

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Chander, G	2002	36	S135	Hepatology	
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Foy, E	2003	300	1145	Science	HCAPLUS
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Llinas-Brunet, M	1998	8	2719	Bioorg Med Chem Lett	HCAPLUS
Llinas-Brunet, M	2000	10	2267	Bioorg Med Chem Lett	HCAPLUS
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Neumann, A	1998	282	103	Science	HCAPLUS
Pause, A	2003	278	20374	J Biol Chem	HCAPLUS
Poupart, M	2001	66	4743	J Org Chem	HCAPLUS
Reed, K	2000	242	55	Curr Top Microbiol I	HCAPLUS
Schechter, I	1967	27	157	Biochem Biophys Res	HCAPLUS
Steinkuhler, C	1998	37	8899	Biochemistry	MEDLINE
Tan, S	2002	1	867	Nature Rev Drug Disc	HCAPLUS

Tsantrizos, Y	2003	42	1356	Angew Chem Int Edn E	HCAPLUS
Zeuzem, S	2001	120	1438	Gastroenterology	HCAPLUS

L41 ANSWER 17 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:725652 HCAPLUS
DOCUMENT NUMBER: 133:296659
ENTRY DATE: Entered STN: 13 Oct 2000
TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus
INVENTOR(S): Tsantrizos, Youla S.; Cameron, Dale R.; Faucher, Anne-marie; Ghiro, Elise; Goudreau, Nathalie; Halmos, Teddy; Llinas-brunet, Montse
PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.
SOURCE: PCT Int. Appl., 154 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: C07K005-08
SECONDARY: C07K005-078; A61K038-05; A61K038-06; A61P031-14
CLASSIFICATION: 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 15
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

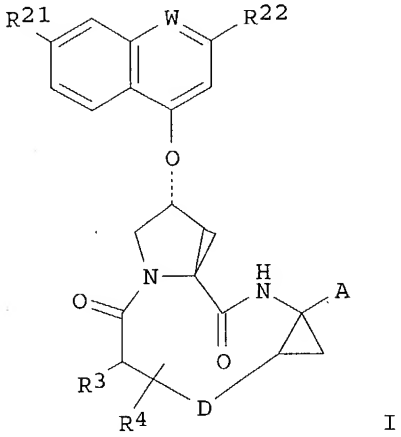
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059929	A1	20001012	WO 2000-CA353	20000403
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1169339	A1	20020109	EP 2000-913999	20000403
EP 1169339	B1	20040929		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000009599	A	20020115	BR 2000-9599	20000403
TR 200102878	T2	20020121	TR 2001-200102878	20000403
EE 200100516	A	20021216	EE 2001-516	20000403
NZ 515286	A	20040227	NZ 2000-515286	20000403
EP 1437362	A1	20040714	EP 2004-9264	20000403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
BG 105970	A	20020531	BG 2001-105970	20011002
HR 2001000720	A1	20021231	HR 2001-720	20011004
NO 2001004857	A	20011031	NO 2001-4857	20011005
PRIORITY APPLN. INFO.:			US 1999-128011P	P 19990406
			EP 2000-913999	A3 20000403
			WO 2000-CA353	W 20000403

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000059929	ICM	C07K005-08
	ICS	C07K005-078; A61K038-05; A61K038-06; A61P031-14

OTHER SOURCE(S): MARPAT 133:296659

GRAPHIC IMAGE:



I

ABSTRACT:
Macrocyclic peptides I [W = CH or N; R21 = H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy, or an amino group; R22 = H, halo, alkyl, cycloalkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkyl, aryl or heteroaryl; R3 = hydroxy, NH2, aryl- or heteroarylamino, NHCOR32, CONHR32, CO2R32, where R32 is alkyl or cycloalkyl; D is a 5 to 10-atom saturated or unsatd. alkylene chain optionally containing one to three heteroatoms independently selected from: O, S, or NH or substituted imino; R4 = H or from one to three substituents at any carbon atom of chain D; A is an amide or carboxylic acid group or a pharmaceutically acceptable salt or ester; two diastereomers may exist at the cyclopropane moiety] were prepared which are active in-vitro and in cellular assays against the NS3 protease of the hepatitis C virus . Thus, macrocyclic peptide I [W = N; R21, R22, R4 = H; A = CO2H; R3CH-D = (S)-(Me3CO2CNH)CH(CH2)3CH:CH(CH2)2-E (syn to acid)] was prepared and showed IC50 > 0.1 μM in the full-length NS3-NS4A heterodimer protein fluorogenic assay.

SUPPL. TERM:	cyclic peptide prepn hepatitis C virus inhibitor
INDEX TERM:	Hepatitis C virus Immunomodulators (preparation of macrocyclic peptides active against the hepatitis C virus)
INDEX TERM:	Macrocyclic compounds Peptides, preparation ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of macrocyclic peptides active against the hepatitis C virus)
INDEX TERM:	Interferons ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (preparation of macrocyclic peptides active against the hepatitis C virus)
INDEX TERM:	300831-32-7P 300831-33-8P 300831-34-9P 300831-79-2P 300831-80-5P 300831-81-6P 300831-82-7P 300831-83-8P 300831-84-9P 300831-85-0P 300831-86-1P 300831-87-2P

300831-88-3P 300831-89-4P 300831-90-7P 300831-91-8P
300831-92-9P 300831-93-0P 300831-94-1P 300831-95-2P
300831-96-3P 300831-97-4P 300831-98-5P 300831-99-6P
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300832-95-5P 300832-96-6P 300832-97-7P 300832-98-8P
300832-99-9P 300833-00-5P 300833-01-6P 300833-02-7P
301188-00-1P
ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 37259-58-8, Serine protease
ROLE: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 62-56-6, Thiourea, reactions 78-39-7, Triethyl orthoacetate 79-22-1, Methyl chloroformate 105-56-6, Ethyl cyanoacetate 288-13-1, Pyrazole 288-32-4, Imidazole, reactions 536-90-3, m-Anisidine 541-16-2, Di-tert-butyl malonate 543-27-1, Isobutyl chloroformate 563-80-4, 3-Methyl-2-butanone 591-08-2, n-Acetylthiourea 598-52-7, n-Methylthiourea 625-53-6, n-Ethylthiourea 696-59-3, 2,5-Dimethoxytetrahydrofuran 822-36-6, 4-Methylimidazole 934-60-1, 6-Methylpicolinic acid 1068-90-2, Diethyl acetamidomalonate 1113-41-3, L-Penicillamine 1113-59-3, 3-Bromopyruvic acid 1119-51-3, 4-Pentenyl bromide 1719-76-2, Isopropylthiourea 2385-77-5 2592-18-9 2695-48-9, 8-Bromo-1-octene 3282-30-2, Pivaloyl chloride 4285-48-7 7554-65-6, 4-MethylPyrazole 10387-40-3, Potassium thioacetate 13726-85-7 16982-21-1, Ethyl thiooxamate 22059-22-9, Acetamidoxime 29681-39-8 50413-30-4 50715-28-1 82121-05-9, 4-Hydroxy-7-methoxyquinoline 85866-02-0, 7-Octene-1,2-diol 90719-32-7 102195-79-9 113240-46-3,

Malonic acid monoallyl ester 126690-67-3 204711-97-7
259214-64-7 259214-73-8 300831-45-2 300831-47-4
300831-50-9 300831-58-7 300831-62-3 300831-65-6
300831-67-8
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 616-47-7P, 1-Methylimidazole 3350-20-7P 17206-61-0P,
6-Heptenal 19967-55-6P 20485-43-2P 27191-09-9P,
m-Anisidine hydrochloride 29082-92-6P 31642-67-8P,
8-Nonenoic acid 42465-53-2P 55327-87-2P,
Acetamidomalonic acid 72086-72-7P 79479-07-5P
99071-95-1P 112380-21-9P 112380-22-0P 126125-54-0P
156589-82-1P 300830-79-9P 300830-80-2P 300830-81-3P
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300831-74-7P 300831-75-8P 300831-76-9P 300831-77-0P
300831-78-1P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 300831-11-2P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(preparation of macrocyclic peptides active against the hepatitis C virus)

INDEX TERM: 768-94-5, Amantadine 36791-04-5, Ribavirin 42613-29-6,
Helicase 81669-70-7, Metalloprotease
ROLE: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of macrocyclic peptides active against the hepatitis C virus)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S): (1) Boehringer Ingelheim Ca Ltd; WO 9907733 A 1999 HCAPLUS

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Boehringer Ingelheim Ca	1999			WO 9907733 A	HCAPLUS

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L41 ANSWER 18 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2004098430 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14988742
TITLE: Gateways to clinical trials.
AUTHOR: Bayes M; Rabasseda X; Prous J R
CORPORATE SOURCE: Prous Science, PO Box 540, 08080 Barcelona, Spain.. mbayes@prous.com
SOURCE: Methods and findings in experimental and clinical pharmacology, (2004 Jan-Feb) 26 (1) 53-84. Ref: 200 Journal code: 7909595. ISSN: 0379-0355.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040302
Last Updated on STN: 20040510
Entered Medline: 20040507

AB Gateways to Clinical Trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies Knowledge Area of Prous Science Integrity, the drug discovery and development portal, http://integrity.prous.com. This issue focuses on the following selection of drugs: Abetimus sodium, Ad5-FGF4, adeno-Interferon gamma, AE-941, AERx, alemtuzumab, alicaforsen sodium, almotriptan, alpharadin, anakinra, anatumomab mafenatox, ANG-453, anti-CTLA-4 Mab, AP-12009, aprepitant, aripiprazole, arsenic trioxide, astemizole, atlizumab, atomoxetine hydrochloride; Bevacizumab, BG-9928, BMS-188667, botulinum toxin type B, BufferGel; Caffeine, CDP-870, cetuximab, cilomilast, **ciluprevir**, clofarabine, continuous erythropoiesis receptor activator, CP-461; Darbepoetin alfa, deferasirox, desloratadine, desoxyepothilone B, diflomotecan, dolasetron, drotrecogin alfa (activated), duloxetine hydrochloride; ED-71, efalizumab, efaproxiral sodium, EKB-569, eletriptan, EMD-72000, enfuvirtide, erlotinib hydrochloride, escitalopram oxalate, etoricoxib; Fampridine, ferumoxytol, fondaparinux sodium; Gadofosveset sodium, gastrazole, gefitinib, gemtuzumab ozogamicin, gepirone hydrochloride glutamine; hLM609, HSPPC-96, human insulin; IDD-1, imatinib mesylate, indisulam, inhaled insulin, ixabepilone; Keratinocyte growth factor; Lapatinib, laquinimod, LDP-02, LE-SN38, levetiracetam, levosimendan, licofelone, liposomal doxorubicin, liposomal NDDP, lopinavir, lumiracoxib, LY-156735; **Morphine** hydrochloride, **morphine**-6-glucuronide, motexafin gadolinium, MS-27-275, MVA-5T4, MVA-Muc1-IL-2; Nemifitide ditriflutate, neridronic acid nitronaproxen, NSC-683864, NSC-703940, NVP-LAF-237; Oblimersen sodium, ocinaplon, oncomyc-NG, OPC-28326, ortataxel, ospemifene; Palonosetron hydrochloride, PEG-filgrastim peginterferon alfa-2(a), peginterferon alfa-2b, pegsunercept, pemetrexed disodium, pregabalin, prilocaine, pyridoxamine; RDP-58, recombinant glucagon-like peptide-1 (7-36) amide, recombinant human ApoA-I milano/phospholipid complex; SB-715992, soblidotin, sodium dichloroacetate, St. John's Wort extract; TAS-102, terfenadine, TG-1024, TG-5001, 4'-Thio-ara-C, tipranavir, topixantrone hydrochloride, trabectedin, transdermal selegiline, trimethoprim, troxacitabine, TT-232; Vatalanib succinate, vinflunine; Ximelagatran; Ziprasidone hydrochloride, Zoledronic acid monohydrate.

AB Gateways to Clinical Trials is a guide to the most recent clinical trials

in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies Knowledge Area of Prous Science Integrity, the drug discovery and development portal, http://integrity.prous.com. This issue focuses on the following selection of drugs: Abetimus sodium, Ad5-FGF4, adeno-Interferon gamma, AE-941, AERx, alemtuzumab, alicaforsen sodium, almotriptan, alpharadin, anakinra, anatumomab mafenatox, ANG-453, anti-CTLA-4 Mab, AP-12009, aprepitant, aripiprazole, arsenic trioxide, astemizole, atlizumab, atomoxetine hydrochloride; Bevacizumab, BG-9928, BMS-188667, botulinum toxin type B, BufferGel; Caffeine, CDP-870, cetuximab, cilomilast, **ciluprevir**, clofarabine, continuous erythropoiesis receptor activator, CP-461; Darbepoetin alfa, deferasirox, desloratadine, desoxyepothilone B, diflomotecan, dolasetron, drotrecogin alfa (activated), duloxetine hydrochloride; ED-71, efalizumab, efaproxiral sodium, EKB-569, eletriptan, EMD-72000, enfuvirtide, erlotinib hydrochloride, escitalopram oxalate, etoricoxib; Fampridine, ferumoxytol, fondaparinux sodium; Gadofosveset sodium, gastrazole, gefitinib, gemtuzumab ozogamicin, gepirone hydrochloride glutamine; hLM609, HSPPC-96, human insulin; IDD-1, imatinib mesylate, indisulam, inhaled insulin, ixabepilone; Keratinocyte growth factor; Lapatinib, laquinimod, LDP-02, LE-SN38, levetiracetam, levosimendan, licofelone, liposomal doxorubicin, liposomal NDDP, lopinavir, lumiracoxib, LY-156735; **Morphine** hydrochloride, **morphine**-6-glucuronide, motexafin gadolinium, MS-27-275, MVA-5T4, MVA-Muc1-IL-2; Nemifitide ditriflutate, neridronic acid nitronaproxen, NSC-683864, NSC-703940, NVP-LAF-237; Oblimersen sodium, ocinaplon, oncomyc-NG, OPC-28326, ortataxel, ospemifene; Palonosetron hydrochloride, PEG-filgrastim peginterferon alfa-2(a), peginterferon alfa-2b, pegsunercept, pemetrexed disodium, pregabalin, prilocaine, pyridoxamine; RDP-58, recombinant glucagon-like peptide-1 (7-36) amide, recombinant human ApoA-I milano/phospholipid complex; SB-715992, soblidotin, sodium dichloroacetate, St. John's Wort extract; TAS-102, terfenadine, TG-1024, TG-5001, 4'-Thio-ara-C, tipranavir, topixantrone hydrochloride, trabectedin, transdermal selegiline, trimethoprim, troxacitabine, TT-232; Vatalanib succinate, vinflunine; Ximelagatran; Ziprasidone hydrochloride, Zoledronic acid monohydrate.

L41 ANSWER 19 OF 36 MEDLINE on STN

ACCESSION NUMBER:	2004035206 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 14735233
TITLE:	Gateways to clinical trials.
AUTHOR:	Bayes M; Rabasseda X; Prous J R
CORPORATE SOURCE:	Prous Science, Barcelona, Spain.. mbayes@prous.com
SOURCE:	Methods and findings in experimental and clinical pharmacology, (2003 Dec) 25 (10) 831-55. Journal code: 7909595. ISSN: 0379-0355.
PUB. COUNTRY:	Spain
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200404
ENTRY DATE:	Entered STN: 20040122 Last Updated on STN: 20040501 Entered Medline: 20040430

AB Gateways to Clinical Trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies Knowledge Area of Prous Science Integrity, the drug discovery and development portal, http://integrity.prous.com. This issue focuses on the following selection of drugs: Abetimus sodium, adalimumab, alefacept, alemtuzumab,

almotriptan, AMGN-0007, anakinra, anti-CTLA-4 Mab, L-arginine hydrochloride, arzoxifene hydrochloride, astemizole, atazanavir sulfate, atlizumab; Belimumab, BG-9928, binodenoson, bosentan, botulinum toxin type B, bovine lactoferrin, BufferGel; Caspofungin acetate, ciclesonide,cilomilast, **ciluprevir**, clofarabine, CVT-3146; Darbepoetin alfa, desloratadine, diflomotecan, doripenem, dronedarone hydrochloride, drotrecogin alfa (activated), DT388-GM-CSF, duloxetine hydrochloride, E-5564, efalizumab, enfuvirtide, esomeprazole magnesium, estradiol acetate, ETC-642, exenatide, exisulind, ezetimib; Febuxostat; Gallium maltolate, ganirelix acetate, garenoxacin mesilate, gefitinib; H11, HuMax; IL-15, IDD-1, IGIV-C, imatinib mesylate, ISIS-14803, ITF-1697, ivabradine hydrochloride; KRN-5500; L-365260, levetiracetam, levosimendan, licofelone, linezolid, LJP-1082, lopinavir lumiracoxib; MCC-478, melatonin, **morphine** hydrochloride, **morphine** -6-glucuronide, moxidectin; N-Acetylcarnosine, natalizumab, NM-702, NNC-05-1869, NSC-703940; Ocinaplon OM-89, omalizumab, omeprazole/ sodium bicarbonate, OPC-28326, ospemifene; PEG-filgrastim peginterferon alfa-2a, pegsunercept, pirfenidone, pralmorelin, pregabalin; Recombinant glucagon-like peptide-1 (7-36) amide, repifermin, RSD-1235; S-8184, selodenoson, sodium dichloroacetate, suberanilohydroxamic acid; TAS-102, terfenadine, teriparatide, tipranavir troxacitabine; Ximelagatran; YM-337. (c) 2003 Prous Science

AB Gateways to Clinical Trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies Knowledge Area of Prous Science Integrity, the drug discovery and development portal, http://integrity.prous.com. This issue focuses on the following selection of drugs: Abetimus sodium, adalimumab, alefacept, alemtuzumab, almotriptan, AMGN-0007, anakinra, anti-CTLA-4 Mab, L-arginine hydrochloride, arzoxifene hydrochloride, astemizole, atazanavir sulfate, atlizumab; Belimumab, BG-9928, binodenoson, bosentan, botulinum toxin type B, bovine lactoferrin, BufferGel; Caspofungin acetate, ciclesonide,cilomilast, **ciluprevir**, clofarabine, CVT-3146; Darbepoetin alfa, desloratadine, diflomotecan, doripenem, dronedarone hydrochloride, drotrecogin alfa (activated), DT388-GM-CSF, duloxetine hydrochloride, E-5564, efalizumab, enfuvirtide, esomeprazole magnesium, estradiol acetate, ETC-642, exenatide, exisulind, ezetimib; Febuxostat; Gallium maltolate, ganirelix acetate, garenoxacin mesilate, gefitinib; H11, HuMax; IL-15, IDD-1, IGIV-C, imatinib mesylate, ISIS-14803, ITF-1697, ivabradine hydrochloride; KRN-5500; L-365260, levetiracetam, levosimendan, licofelone, linezolid, LJP-1082, lopinavir lumiracoxib; MCC-478, melatonin, **morphine** hydrochloride, **morphine** -6-glucuronide, moxidectin; N-Acetylcarnosine, natalizumab, NM-702, NNC-05-1869, NSC-703940; Ocinaplon OM-89, omalizumab, omeprazole/ sodium bicarbonate, OPC-28326, ospemifene; PEG-filgrastim peginterferon alfa-2a, pegsunercept, pirfenidone, pralmorelin, pregabalin; Recombinant glucagon-like peptide-1 (7-36) amide, repifermin, RSD-1235; S-8184, selodenoson, sodium dichloroacetate, suberanilohydroxamic acid; TAS-102, terfenadine, teriparatide, tipranavir troxacitabine; Ximelagatran; YM-337. (c) 2003 Prous Science

L41 ANSWER 20 OF 36 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:133738 BIOSIS
DOCUMENT NUMBER: PREV200400132108
TITLE: VX-950, a HCV protease inhibitor, retains potency against BILN-2061 resistant replicon cells.
AUTHOR(S): Lin, Chao [Reprint Author]; Lin, Kai [Reprint Author]; Gates, Cynthia A. [Reprint Author]; Ma, Sue [Reprint Author]; Brennan, Debra [Reprint Author]; Fulghum, John

[Reprint Author]; Hsiao, Hsun-Mei [Reprint Author]; Rao, Govinda [Reprint Author]; Wei, Yunyi [Reprint Author]; Alford, John [Reprint Author]; Perni, Robert B. [Reprint Author]; Kwong, Ann D. [Reprint Author]
CORPORATE SOURCE: Vertex Pharmaceuticals Inc., Cambridge, MA, USA
SOURCE: Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp. 638A. print.
Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American Association for the Study of Liver Diseases.
ISSN: 0270-9139 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 2004
Last Updated on STN: 10 Mar 2004

AB Due to the limited efficacy of current therapies for chronic Hepatitis C virus (HCV) infected patients, more specific and potent anti-HCV drugs are needed. We have been developing small molecule inhibitors of the HCV NS3cntdot4A protease using a **structure**-based, rational drug design process. We recently selected VX-950 as a candidate for clinical development. In this report, we describe resistance studies, using an in vitro replicon system, conducted on VX-950 and **BILN-2061** , another HCV protease inhibitor, which was recently reported to be in clinical trials. Distinct drug-resistant mutations were identified for both protease inhibitors. Mutants that are resistant to **BILN-2061** remain fully sensitive to VX-950. Characterization of enzymatic, kinetic, and anti-viral properties will be presented for mutations that confer resistance to VX-950 or to **BILN-2061.**

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L41 ANSWER 21 OF 36 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:123506 BIOSIS
DOCUMENT NUMBER: PREV200400116725
TITLE: Sensitivity of NS3 serine proteases from various Hepatitis C Virus genotypes to the antiviral compound BILN 2061.
AUTHOR(S): Thibeault, Diane [Reprint Author]; Bousquet, Christiane [Reprint Author]; Gingras, Rock [Reprint Author]; Lagace, Lisette [Reprint Author]; Maurice, Roger [Reprint Author]; White, Peter W. [Reprint Author]; Lamarre, Daniel [Reprint Author]
CORPORATE SOURCE: Boehringer Ingelheim (Canada) Ltd, Laval, PQ, Canada
SOURCE: Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp. 300A. print.

Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American Association for the Study of Liver Diseases.
ISSN: 0270-9139 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004

AB Introduction: Genetic heterogeneity is an important feature of Hepatitis C Virus (HCV) genomes with six known genotypes and more than 50 subtypes. Genotypes 1, 2 and 3 are broadly distributed in patients around the world, whereas the other types are more geographically restricted. The peptidomimetic inhibitor **BILN 2061**, optimized to have a high affinity for genotype 1 NS3 protease, has been reported to reduce viral load in genotype 1 HCV infected individuals. In this study, the ability of **BILN 2061** to inhibit the NS3 proteases from the other widespread genotypes 2 and 3 was assessed. Methods: The NS3 protease domains and the NS3-NS4A proteins of genotypes 1a, 1b, 2ac, 2b and 3a were cloned, expressed in E. coli and purified. Protease activity was evaluated using fluorogenic depsipeptide substrates derived from the amino acid sequence at the NS4A-NS4B and NS5A-NS5B junctions. Results: The activity of the NS3 protease domains revealed no major differences among the various genotypes. For the NS3-NS4A proteins, the catalytic efficiencies of the non-genotype 1 enzymes, although higher than the ones observed for the corresponding protease domains, were similar to that observed for genotype 1 (within 3-fold). Differences in activity observed among genotypes were mainly related to changes in kcat values. Binding constant (Ki) values for **BILN 2061** were similar among non-genotype 1 proteases with Ki's ranging from 80-90 nM for the NS3-NS4A proteins, up to a 60-fold reduction in affinity when compared to genotype 1. Conclusion: The major pharmacophores of **BILN 2061** were optimized for binding to HCV genotype 1 NS3 protease. Thus binding of **BILN 2061** was found to be more sensitive to naturally occurring **polymorphism** of the protease than the unnatural surrogate substrates used in this study. Even though a decreased sensitivity of non-genotype 1 proteases to **BILN 2061** was observed, **BILN 2061** remains a potent inhibitor of the NS3-NS4A protein with Ki values below 100 mM. The in vitro potency in conjunction with the good pharmacokinetics data reported in man suggests that **BILN 2061** may demonstrate antiviral activity in non-genotype 1 HCV infected individuals.

AB Introduction: Genetic heterogeneity is an important feature of Hepatitis C Virus (HCV) genomes with six known genotypes and more than 50 subtypes. Genotypes 1, 2 and 3 are broadly distributed in patients around the world, whereas the other types are more geographically restricted. The peptidomimetic inhibitor **BILN 2061**, optimized to have a high affinity for genotype 1 NS3 protease, has been reported to reduce viral load in genotype 1 HCV infected individuals. In this study, the ability of **BILN 2061** to inhibit the NS3 proteases from the other widespread genotypes 2 and 3 was assessed. Methods: The NS3 protease domains and the NS3-NS4A proteins of genotypes 1a, 1b, 2ac, 2b and 3a were cloned, expressed in E. coli and purified. Protease activity was evaluated using fluorogenic depsipeptide substrates derived from the amino acid sequence at the NS4A-NS4B and NS5A-NS5B junctions. Results: The activity of the NS3 protease domains revealed no major differences among the various genotypes. For the NS3-NS4A proteins, the catalytic efficiencies of the non-genotype 1 enzymes, although higher than the ones

observed for the corresponding protease domains, were similar to that observed for genotype 1 (within 3-fold). Differences in activity observed among genotypes were mainly related to changes in kcat values. Binding constant (Ki) values for **BILN 2061** were similar among non-genotype 1 proteases with Ki's ranging from 80-90 nM for the NS3-NS4A proteins, up to a 60-fold reduction in affinity when compared to genotype 1. Conclusion: The major pharmacophores of **BILN 2061** were optimized for binding to HCV genotype 1 NS3 protease. Thus binding of **BILN 2061** was found to be more sensitive to naturally occurring **polymorphism** of the protease than the unnatural surrogate substrates used in this study. Even though a decreased sensitivity of non-genotype 1 proteases to **BILN 2061** was observed, **BILN 2061** remains a potent inhibitor of the NS3-NS4A protein with Ki values below 100 mM. The in vitro potency in conjunction with the good pharmacokinetics data reported in man suggests that **BILN 2061** may demonstrate antiviral activity in non-genotype 1 HCV infected individuals.

L41 ANSWER 22 OF 36 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:123273 BIOSIS
DOCUMENT NUMBER: PREV200400116587
TITLE: VX-950: A tight-binding HCV protease inhibitor with a superior sustained inhibitory response in HCV replicon cells.
AUTHOR(S): Lin, Kai [Reprint Author]; Gates, Cynthia A. [Reprint Author]; Luong, Yu-Ping [Reprint Author]; Perni, Robert B. [Reprint Author]; Kwong, Ann D. [Reprint Author]
CORPORATE SOURCE: Vertex Pharmaceuticals Inc, Cambridge, MA, USA
SOURCE: Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp. 222A. print.
Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American Association for the Study of Liver Diseases.
ISSN: 0270-9139 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004

AB We have been developing HCV NS3cntdot4A protease inhibitors using a **structure**-based, rational drug design process. In these studies, we compared our clinical candidate, VX-950, to **BILN-2061** , another HCV protease inhibitor in clinical development (2002 AASLD Mtg). VX-950 and **BILN-2061** exhibit inhibition mechanisms that appear kinetically distinct from each another. Additional studies were designed to investigate the effects of these different mechanisms of protease inhibition on replication in a replicon system. HCV replicon cells were incubated with concentrations of VX-950 or **BILN-2061** that were fixed multiples (X10 and X50) of their respective IC50's in the absence of G418. Two days after the addition of compound, the rate of inhibition of HCV replicon RNA was similar for both drugs. In contrast, at late times (12-15 days) after the addition of drug, VX-950 suppressed HCV replicon RNA to dramatically lower levels than **BILN -2061** (typically 1-2 log10). When the same experiment was performed in the presence of G418, more colonies of resistant cells grew in the cultures containing **BILN-2061** than VX-950. These results indicate that VX-950 has a more potent and sustainable antiviral response in HCV replicon cells than **BILN-2061**

. These findings will be discussed, in the context of the different chemical **structures** and enzyme inhibition mechanisms of these two inhibitors.

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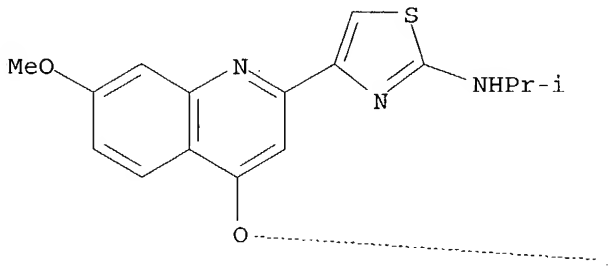
=>
=> d 23-29

L41 ANSWER 23 OF 36 ADISINSIGHT COPYRIGHT (C) 2004 Adis Data Information BV on STN

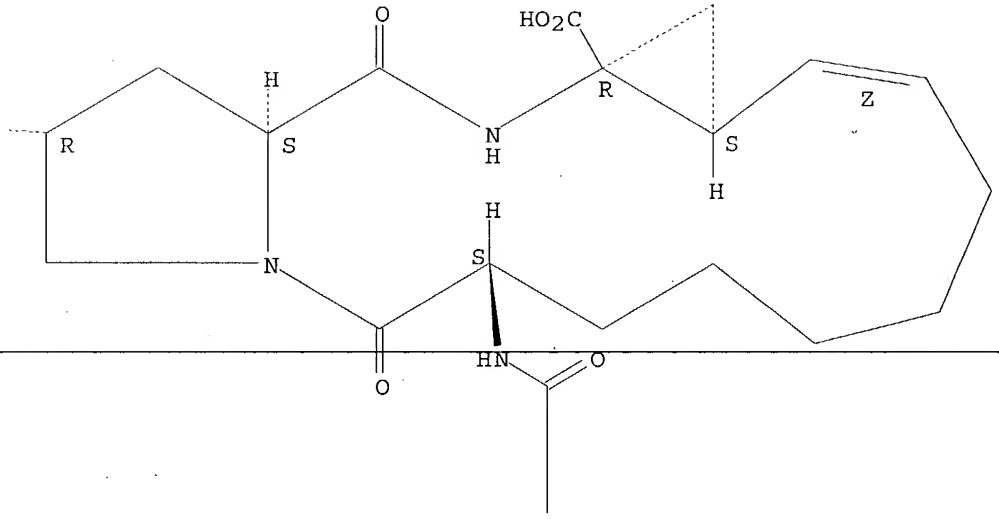
ACCESSION NUMBER: 2002:466 ADISINSIGHT
SOURCE: Adis R&D Insight
DOCUMENT NO: 017325
CHANGE DATE: Jun 1, 2004
GENERIC NAME: **Ciluprevir**
SYNONYM: **BILN 2061; BILN 2061 ZW; BILN-2061**
CHEMICAL NAME: Cyclopropa(e)pyrrolo(1,2-a)(1,4)diazacyclopentadecine-14a(5H)-carboxylic acid, 6-(((cyclopentyloxy)carbonyl)amino)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-((7-methoxy-2-(2-((1-methylethyl)amino)-4-thiazolyl)-4-quinolinyl)oxy)-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)-
MOLECULAR FORMULA: C40 H50 N6 O8 S
CAS REGISTRY NO.: **300832-84-2**
STRUCTURE:

Absolute stereochemistry.
Double bond geometry as shown.

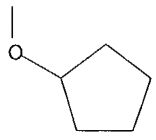
PAGE 1-A



PAGE 1-B



PAGE 2-B



EPHMRA ATC CODE: J5B Antivirals, excluding anti-HIV products
WHO ATC CODE: J05A-E Protease inhibitors
HIGHEST DEV. PHASE: Suspended II

COMPANY INFORMATION
ORIGINATOR: Boehringer Ingelheim (Canada); Boehringer Ingelheim

Pharma KG (Germany)
PARENT: Boehringer Ingelheim

WORD COUNT: 711

L41 ANSWER 24 OF 36 ADISINSIGHT COPYRIGHT (C) 2004 Adis Data Information BV on STN
ACCESSION NUMBER: 2000:1398 ADISINSIGHT
SOURCE: Adis R&D Insight
DOCUMENT NO: 014557
CHANGE DATE: Dec 23, 2003
GENERIC NAME: Research programme: hepatitis C virus NS3 protease inhibitors -Boehringer Ingelheim
SYNONYM: Hepatitis C virus NS3 protease inhibitors research programme -Boehringer Ingelheim
MOLECULAR FORMULA:Unspecified
STRUCTURE:
STRUCTURE DIAGRAM IS NOT AVAILABLE

EPHMRA ATC CODE: J5B Antivirals, excluding anti-HIV products
WHO ATC CODE: J05A-E Protease inhibitors
HIGHEST DEV. PHASE: Preclinical

COMPANY INFORMATION
ORIGINATOR: Boehringer Ingelheim (Canada); Boehringer Ingelheim (Germany)
PARENT: Boehringer Ingelheim

WORD COUNT: 365

L41 ANSWER 25 OF 36 ADISINSIGHT COPYRIGHT (C) 2004 Adis Data Information BV on STN
ACCESSION NUMBER: 1998:10260 ADISINSIGHT
SOURCE: Adis R&D Insight
DOCUMENT NO: 011269
CHANGE DATE: Sep 16, 2004
GENERIC NAME: VX 950
SYNONYM: Hepatitis C virus protease inhibitors research programme - Vertex/Eli Lilly; LY 570310; LY-570310; LY570310
MOLECULAR FORMULA:Unspecified
STRUCTURE:
STRUCTURE DIAGRAM IS NOT AVAILABLE

EPHMRA ATC CODE: J5B Antivirals, excluding anti-HIV products
WHO ATC CODE: J05A-E Protease inhibitors
HIGHEST DEV. PHASE: Phase I

COMPANY INFORMATION
ORIGINATOR: Eli Lilly (United States); Vertex Pharmaceuticals (United States)
PARENT: Eli Lilly; Vertex Pharmaceuticals

OTHER SOURCES: 809035665; 809038928
WORD COUNT: 1068

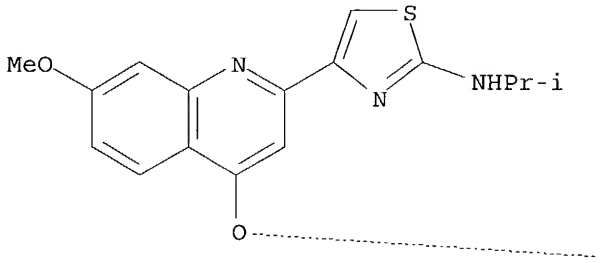
L41 ANSWER 26 OF 36 IMSRESEARCH COPYRIGHT 2004 IMSWORLD on STN

ACCESSION NUMBER: 2002:1036 IMSRESEARCH
SOURCE: R&D Focus, (16 Feb 2004)
GENERIC NAME: **ciluprevir; ciluprevir**

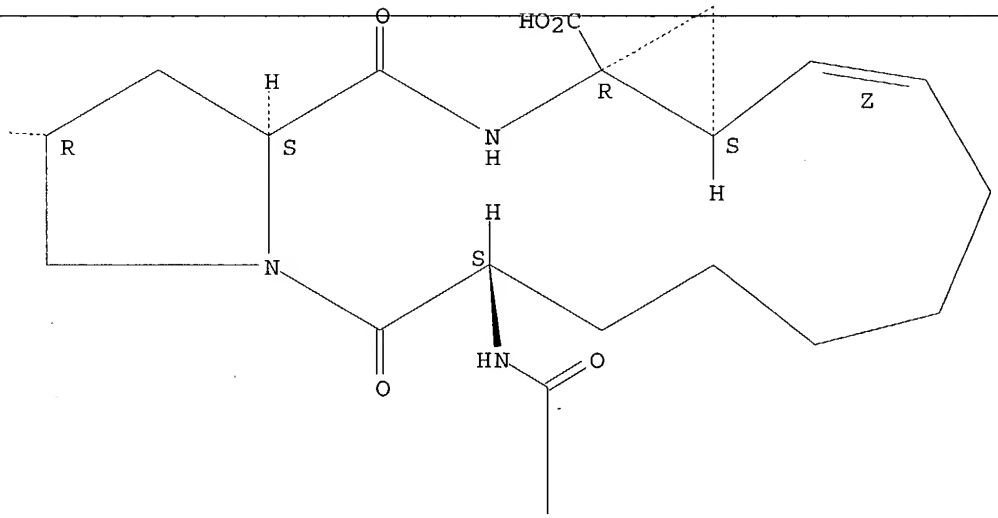
REFERENCE: pINN
LABORATORY NAME: **BILN 2061; BILN 2061ZW**
CHEMICAL NAME: (2R,6S,12Z,13aS,14aR,16aS)-6-[[(cyclopentyloxy)carbonyl]amino]-1,2, 3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2- [(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-cy clopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxy lic acid
CAS REGISTRY NO.: **300832-84-2**
STRUCTURE:

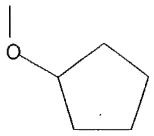
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B





DERIVATIVE(S): **300832-84-2ciluprevir**
CLASSIFICATION: J5B Antivirals, Excluding Anti-HIV Products
HIGHEST DEV. PHASE: Phase II (40)

COMPANY INFORMATION:

Type	Company	Nationality
Originator	Boehringer Ingelheim	Germany, Federal Republic of
Assignee	Boehringer Ingelheim	

L41 ANSWER 27 OF 36 IMSRESEARCH COPYRIGHT 2004 IMSWORLD on STN

ACCESSION NUMBER: 2002:50 IMSRESEARCH
SOURCE: R&D Focus, (21 Jun 2004)
LABORATORY NAME: VX 950; LY 570310
STRUCTURE:
STRUCTURE DIAGRAM IS NOT AVAILABLE
CLASSIFICATION: J5B Antivirals, Excluding Anti-HIV Products
HIGHEST DEV. PHASE: Phase I (30)

COMPANY INFORMATION:

Type	Company	Nationality	Region
Originator	Vertex	United States	
Licensee	Lilly	United States	
Licensee	Mitsubishi Pharma	Japan	Japan; Far East
Other	Chiron	United States	

L41 ANSWER 28 OF 36 PHAR COPYRIGHT 2004 PJB on STN
AN 29819 PHAR
DN 035871
CN **ciluprevir**
CN **BILN-2061**
CN Cyclopropa(e)pyrrolo(1,2-a)(1,4)diazacyclopentadecine-14a(5H)-carboxylic acid,6-(((cyclopentyloxy)carbonyl)amino)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-((7-methoxy-2-(2-((1-methylethyl)amino)-4-thiazolyl)-4-quinolinyl)oxy)-5,16-dioxo-,(2R,6S,12Z,13aS,14aR,16aS)-
RN **300832-84-2**
STA Active

CO

Type	Company Name (Country)	Development Status
Originator	Boehringer Ingelheim (Germany)	Phase II Clinical Trial

SO Pharmaprojects. PJB Publications Ltd., Richmond, Surrey, UK
TX **Ciluprevir** (**BILN-2061**) is a selective inhibitor of the hepatitis-C virus (HCV) NS3 serine protease, under development by Boehringer Ingelheim for the treatment of HCV infection (53rd Meet Am Assoc Study Liv Dis (Boston), 2002, Abs 464).ClinicalPhase IIIPhase III trials are expected by the end of 2004 (18th Int Symp Med Chem (Copenhagen), 2004, Abs L29).Phase II It is in Phase II trials (Nature Rev Drug Disc, 2002, 1, 867).Phase IIn healthy males, single doses of 5-2400mg po produced no serious adverse effects. The MTD was 2000mg; higher doses caused minor intestinal adverse effects. It had a pharmacokinetic profile suitable for bid dosing of >200mg with or without food (53rd Meet Am Assoc Study Liv Dis (Boston), 2002, Abs 800). In 31 patients with HCV genotype 1 infection and minimal liver fibrosis (mean age 47yr; 48% HCV treatment-naive), 7/9 subjects given **ciluprevir** 25mg po bid x2 days, 8/8 given 200 and 8/8 receiving 500mg po bid x2 days showed a >1log decrease in serum HCV RNA levels. Levels returned to baseline 1-7 days after stopping therapy. No difference was seen in responsiveness of interferon-naive and interferon-resistant patients. No safety issues were identified (ibid, Abs 866). In a randomized, double-blind, placebo-controlled study in 10 patients with HCV genotype 1 and significant liver fibrosis, **ciluprevir** 200mg po bid x2 days produced >2log reduction in serum HCV RNA levels in all 8 patients treated. 2 patients had a decrease of >3log (ibid, Abs 563). In a randomized study, 10 HCV genotype 2- and 3- patients with minimal or no liver fibrosis were given **ciluprevir** 500mg bid po solution or placebo x2 days, with 12-day follow-up. 4/8 patients given **ciluprevir** showed a 1log reduction in HCV RNA, with no detectable difference between genotypes. A further **ciluprevir**-treated patient had a weak response. There were no safety issues (53rd Meet Am Assoc Study Liver Dis (Boston), 2003).Preclinicalln the cell-based replicon assay it showed inhibition of HCV RNA replication at low nM levels. It is orally bioavailable in various animal species. It had Ki values of 0.3 and 0.66nM for the NS3 proteases of HCV genotypes 1a and 1b, respectively (ibid, Abs 464). Updated by AZ on 16/8/2004.
DSTA World: Phase II Clinical Trial
Germany: Phase II Clinical Trial
CC J5Z Antiviral, other
CT Indication: Infection, hepatitis-C virus
ORGM CH-SY (Chemical, synthetic)
RTE A-PO (Alimentary, po)
RDAT 20040120 RNTE ##Act##Name Granted **BILN-2061**
20030515 ##Act##New Chemical Structure New
20030509 ##Act##New Product
NRAT 6:Novelty Rating - Leading Compound
MRAT 3:Market Rating - US$ 2001-5000 million
SRAT 0:Speed Rating - Not available
TRAT 0:Total Rating - Total Rating unavailable
PHCD PR-NS3-AN; NS3 protease inhibitor; Enzyme, Hydrolase, NS3 protease inhibitor; NS3-4A protease inhibitor; Protease inhibitor, NS3; E-HY-PR-NS3-AN; 3.4.21.
PHCD E; E-AN; E-HY; E-HY-AN; E-HY-PR; E-HY-PR-AN; E-HY-PR-NS3; E-HY-PR-NS3-AN; HY; HY-AN; HY-PR; HY-PR-AN; HY-PR-NS3; HY-PR-NS3-AN; PR; PR-AN; PR-NS3; PR-NS3-AN; NS3; NS3-AN.

PHK

Model	Parameter	Values	Units
Human (po)	MTD	2000	mg

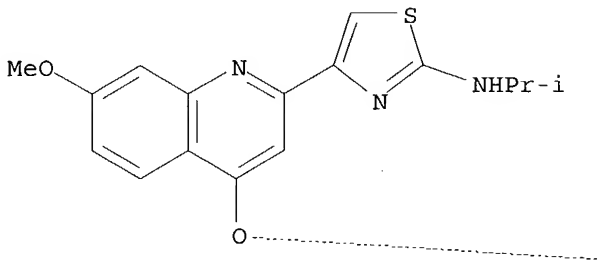
LN

Therapy (CC)	Pharmacology (PHCD)	Status (DSTC)
J5Z	PR-NS3-AN	C2

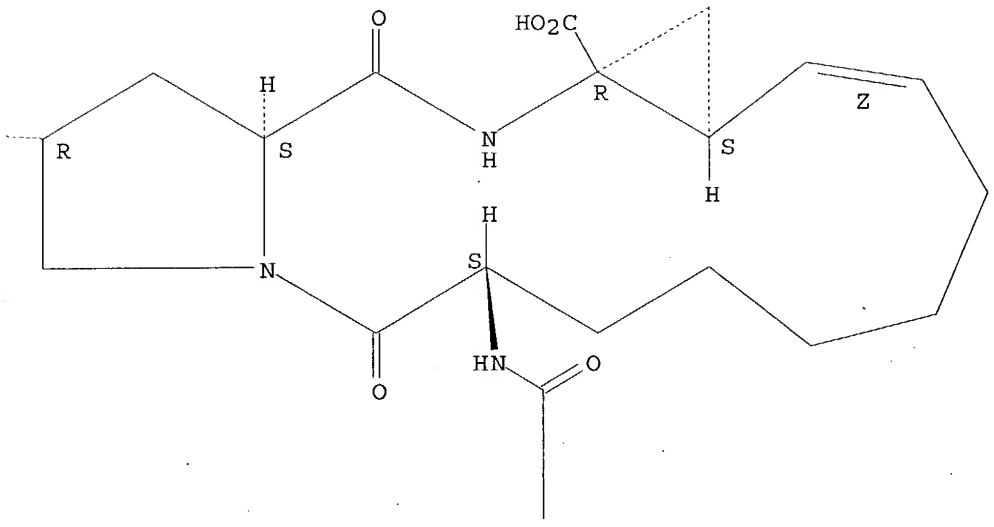
LCDAT 20040816: AZ : Phase III plans reported at 18th ISMC

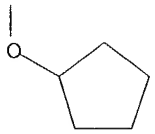
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B





L41 ANSWER 29 OF 36 PHAR COPYRIGHT 2004 PJB on STN
AN 15090 PHAR
DN 026229
CN VX-950
CN Pharmaprojects No. 5437
CN HCV protease inhib, Lilly
CN LY-570310
CN HCV protease inhib, Vertex
STA Active

CO

Type	Company Name (Country)	Development Status
Originator	Vertex Pharmaceuticals (United States)	Phase I Clinical Trial
Licensee	Mitsubishi Pharma (Japan)	Preclinical

SO Pharmaprojects. PJB Publications Ltd., Richmond, Surrey, UK
TX VX-950 is an NS3-4A serine protease inhibitor, under development by Vertex Pharmaceuticals for the treatment of chronic hepatitis- C virus (HCV) infection.MarketingVX-950 was identified as part of a collaboration between Vertex and Lilly, and was to be co-promoted in the US, with Lilly responsible for formulation, global marketing and development (Ann Rep, Vertex, 1999). However, the agreement was restructured and Vertex will lead development and commercialization, with Lilly retaining a financial interest (Press release, Vertex, 2 Jan 2003). It is exclusively licensed to Mitsubishi Pharma for development and commercialization in Japan and certain Far Eastern countries (Press release, Vertex, 14 Jun 2004). Chiron was granted limited rights to review VX-950 for licensing (Press release, Chiron, 7 Nov 2003).ClinicalPhase IA placebo-controlled Phase Ib trial to evaluate the safety, tolerability and pharmacokinetics of up to 14 days of dosing with VX-950 in healthy volunteers and HCV-infected patients is expected in the 4th qtr of 2004, with results expected in the 1st half of 2005 (Press release, Vertex, 7 Sep 2004; 17th Bear Stearns Healthcare Conf (New York), 2004). In a Phase Ia trial in 35 healthy subjects in Europe to assess safety, tolerability and pharmacokinetics in escalating single doses, VX-950 25-1250mg did not reach MTD and no DLTs were identified. However, blood concentrations of VX-950 exceeded levels showing antiviral activity in preclinical studies, and at certain doses these concentrations were maintained for >12hr. Analysis of clinical and preclinical pharmacokinetics suggests liver concentrations 10-30x above the replicon IC50 were achievable in humans (Press release, Vertex, 7 Sep 2004).PreclinicalIn an HCV replicon assay system, treatment of HCV replicon cells with VX-950 x9 days reduced HCV RNA by almost 10000x. HCV replicon cells treated with VX-950 x13 days exhibited viral clearance at day 13, and no rebound of HCV RNA was observed at day 27. In a novel HCV protease expression model, VX-950 po resulted in a significant, dose-dependent inhibition of an HCV-protease

enzyme-dependent signal. In untreated controls, high concentrations of active HCV protease enzyme over 7 days were associated with significant liver damage; however, treatment with VX-950 for the initial 3 days resulted in sharply reduced liver damage. VX-950 was also able to inhibit HCV replicons containing the dominant mutation observed for **BILN-2061** (qv) to the same degree as wild-type replicons (Press release, Vertex, 27 Oct 2003). Updated by AG on 29/9/2004.

DSTA World: Phase I Clinical Trial
Japan: Preclinical
United States: Preclinical

CC J5Z Antiviral, other

CT Indication: Infection, hepatitis-C virus

ORGM CH-SY (Chemical, synthetic)

RTE A-PO (Alimentary, po)

RDAT 20040614 RNTE ##Act##New Licensee Mitsubishi Pharma
20040609 ##Act##Status changed Phase I Clinical Trial
20020107 ##Act##Compound identified HCV protease inhib, Vertex
20001009 ##Act##Development Continuing
19990914 ##Est##No Development Reported
19970718 ##Est##New Product

NRAT 5:Novelty Rating - 2nd, 3rd or 4th Compound

MRAT 3:Market Rating - US$ 2001-5000 million

SRAT 2:Speed Rating - Slower than Average

TRAT 10:Total Rating - Total Rating

PHCD PR-NS3-AN; NS3 protease inhibitor; Enzyme, Hydrolase, NS3 protease inhibitor; NS3-4A protease inhibitor; Protease inhibitor, NS3; E-HY-PR-NS3-AN; 3.4.21.

PHCD E; E-AN; E-HY; E-HY-AN; E-HY-PR; E-HY-PR-AN; E-HY-PR-NS3; E-HY-PR-NS3-AN; HY; HY-AN; HY-PR; HY-PR-AN; HY-PR-NS3; HY-PR-NS3-AN; PR; PR-AN; PR-NS3; PR-NS3-AN; NS3; NS3-AN.

LN

Therapy (CC)	Pharmacology (PHCD)	Status (DSTC)
J5Z	PR-NS3-AN	C1

LCDAT 20040929: AG : Expected timing of results from planned Phase IIb trial reported

STRUCTURE DIAGRAM IS NOT AVAILABLE

=> d ibib abs 30-31

L41 ANSWER 30 OF 36 TOXCENTER COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:53173 TOXCENTER
COPYRIGHT: Copyright (c) 2004 The Thomson Corporation.
DOCUMENT NUMBER: PREV200400116586
TITLE: Antiviral effect of **BILN 2061**, a novel HCV serine protease inhibitor, after oral treatment over 2 days in patients with chronic hepatitis C, non-genotype 1
AUTHOR(S): Reiser, Markus [Reprint Author]; Hinrichsen, Holger; Benhamou, Yves; Sentjens, Roel; Wedemeyer, Heiner; Calleja, Luis; Forns, Xavier; Croenlein, Jens; Yong, Chan; Nehmiz, Gerhard; Steinmann, Gerhard
CORPORATE SOURCE: Medizinische Universitaetsklinik, Bochum, Germany
SOURCE: Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp.

221A. print.
Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases Boston, MA, USA October 24-28, 2003 American Association for the Study of Liver Diseases.
ISSN: 0270-9139 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
FILE SEGMENT: BIOSIS
OTHER SOURCE: BIOSIS 2004:123272
LANGUAGE: English
ENTRY DATE: Entered STN: 20040309
Last Updated on STN: 20040309

AB Introduction: **BILN 2061** is a potent and specific inhibitor of the HCV serine protease in-vitro and in patients infected with genotype 1 (GT 1) as recently reported. In a first exploratory trial, the effect of a 2-day oral treatment with **BILN 2061** was investigated in GT 2 and GT 3 patients with minimal liver fibrosis. Methods: In a randomized, double-blind group comparison, 10 male patients with HCV other than GT 1 (InnoLiPA) and no or minimal liver fibrosis (Ishak 0-2) were administered 500 mg **BILN 2061** or placebo in an oral solution (randomized 8:2) b.i.d. over 2 days. Virus load (VL) was measured as HCV RNA by Cobas Amplicor HCV Monitor v2.0. Results: Mean age of all 10 patients was 37+-7 years. HCV genotypes were GT 2 (3 patients) and GT 3 (7 patients). 9/10 patients were naive for anti-HCV therapy. All patients completed the study and were followed up for 12+-2 days. VL decreased by gtoreq1 LOG10 unit in 4/8 patients treated with 500mg **BILN 2061** b.i.d., without detectable difference between GTs 2 and 3. A weak response was observed in 1 **BILN 2061**-treated patient, whereas 3/8 **BILN 2061**-treated patients and 2/2 patients given placebo experienced no response. The largest VL decrease was observed in the one patient with GT 2 HCV that had been previously treated with anti-HCV therapy. However HCV-RNA was still detectable. After end of treatment, VL returned to baseline levels within 1-7 days. No adverse events were reported. Liver function tests did not change during treatment. Vital signs, routine laboratory and ECG did not show relevant drug-induced changes. Tolerability was rated "good" by the investigators in 9 patients and "satisfactory" in 1 **BILN 2061** -treated patient. Conclusion: **BILN 2061**, given p.o. over 2 days at 500 mg b.i.d., demonstrated antiviral activity in 5/8 non-GT-1 in patients. In contrast to our previous results in GT-1 patients, the antiviral activity was not uniform and less pronounced. No safety issues were identified among the 8 patients exposed to **BILN 2061.**

L41 ANSWER 31 OF 36 TOXCENTER COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:277977 TOXCENTER
COPYRIGHT: Copyright (c) 2004 The Thomson Corporation.
DOCUMENT NUMBER: PREV200200618388
TITLE: Tolerability and pharmacokinetics of **BILN 2061**, a novel HCV serine protease inhibitor, after oral single doses of 5 to 2400 mg in healthy male subjects
AUTHOR(S): Narjes, Hans [Reprint author]; Yong, Chan Loi; Staehle, Hildegard [Reprint author]; Steinmann, Gerhard [Reprint author]
CORPORATE SOURCE: Boehringer Ingelheim Pharma KG, Bibérach, Germany
SOURCE: Hepatology, (October, 2002) Vol. 36, No. 4 Part 2, pp. 363A. print.
Meeting Info.: 53rd Annual Meeting on the Liver BOSTON,

MA, USA November 01-05, 2002
CODEN: HPTLD9. ISSN: 0270-9139.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
FILE SEGMENT: BIOSIS
OTHER SOURCE: BIOSIS 2002:618388
LANGUAGE: English
ENTRY DATE: Entered STN: 20021210
Last Updated on STN: 20021210

=> d ibib abs 32-
YOU HAVE REQUESTED DATA FROM 5 ANSWERS - CONTINUE? Y/(N):y

L41 ANSWER 32 OF 36 USPATFULL on STN
ACCESSION NUMBER: 2004:240310 USPATFULL
TITLE: Viral polymerase inhibitors
INVENTOR(S): Poupart, Marc-Andre, Laval, CANADA
Beaulieu, Pierre Louis, Rosemere, CANADA
Rancourt, Jean, Laval, CANADA
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Ingelheim, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004186125	A1	20040923
APPLICATION INFO.:	US 2004-755544	A1	20040112 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-441674P	20030122 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BOEHRINGER INGELHEIM CORPORATION, 900 RIDGEBURY RD, P O BOX 368, RIDGEFIELD, CT, 06877
NUMBER OF CLAIMS: 42
EXEMPLARY CLAIM: 1
LINE COUNT: 2152
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An isomer, enantiomer, diastereoisomer or tautomer of a compound, represented by formula I: ##STR1##

wherein wherein A, B, R.sup.2, R.sup.3, M.sup.1, M.sup.2, M.sup.3, M.sup.4, Y.sup.1 and Z are as defined in claim 1, or a salt thereof, as an inhibitor of HCV NS5B polymerase.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L41 ANSWER 33 OF 36 USPATFULL on STN
ACCESSION NUMBER: 2004:221854 USPATFULL
TITLE: Viral polymerase inhibitors
INVENTOR(S): Beaulieu, Pierre Louis, Rosemere, CANADA
Brochu, Christian, Blainville, CANADA
Chabot, Catherine, Terrebonne, CANADA
Jolicoeur, Eric, Laval, CANADA
Kawai, Stephen, Montreal, CANADA
Poupart, Marc-Andre, Laval, CANADA
Tsantrizos, Youla S., St. Laurent, CANADA
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Ingelheim, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004171626	A1	20040902
APPLICATION INFO.:	US 2004-755256	A1	20040112 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-441871P	20030122 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BOEHRINGER INGELHEIM CORPORATION, 900 RIDGEBURY RD, P O BOX 368, RIDGEFIELD, CT, 06877
NUMBER OF CLAIMS: 76
EXEMPLARY CLAIM: 1
LINE COUNT: 6508
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An isomer, enantiomer, diastereoisomer or tautomer of a compound, represented by formula I: ##STR1##

wherein wherein A, B, R.sup.2, R.sup.3, L, M.sup.1, M.sup.2, M.sup.3, M.sup.4, Y.sup.1, Y.sup.0, Z and Sp are as defined in claim 1, or a salt thereof, as an inhibitor of HCV NS5B polymerase.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L41 ANSWER 34 OF 36 USPATFULL on STN
ACCESSION NUMBER: 2004:108172 USPATFULL
TITLE: Compounds with the bicyclo[4.2.1]nonane system for the treatment of flavivridae infections
INVENTOR(S): Wang, Peiyuan, Lilburn, GA, UNITED STATES
Stuyver, Lieven J., Snellville, GA, UNITED STATES
Watanabe, Kyoichi A., Stone Mountain, GA, UNITED STATES
Hassan, Abdalla, Chamblee, GA, UNITED STATES
Chun, Byoung-Kwon, Duluth, GA, UNITED STATES
Hollecker, Laurent, Atlanta, GA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004082574	A1	20040429
APPLICATION INFO.:	US 2003-632997	A1	20030801 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-453716P	20020801 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KING & SPALDING, 191 PEACHTREE STREET, N.E., ATLANTA, GA, 30303-1763
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 3637
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The disclosed invention is a bicyclo[4.2.1]nonane and its pharmaceutically acceptable salt or prodrug, and its composition and method of use to treat Flaviviridae (Hepacivirus, Flavivirus, and Pestivirus) infections in a host, including animals, and especially humans.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L41 ANSWER 35 OF 36 USPATFULL on STN
ACCESSION NUMBER: 2004:101717 USPATFULL
TITLE: 2'-C-methyl-3'-O-L-valine ester ribofuranosyl cytidine for treatment of flaviviridae infections
INVENTOR(S): Sommadossi, Jean-Pierre, Cambridge, MA, UNITED STATES
LaColla, Paola, Cagliari, ITALY

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004077587	A1	20040422
APPLICATION INFO.:	US 2003-607909	A1	20030627 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-392351P	20020628 (60)
	US 2003-466194P	20030428 (60)
	US 2003-470949P	20030514 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KING & SPALDING, 191 PEACHTREE STREET, N.E., ATLANTA, GA, 30303-1763
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 3396
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The 3'-L-valine ester of β-D-2'-C-methyl-ribofuranosyl cytidine provides superior results against flaviviruses and pestiviruses, including hepatitis C virus. Based on this discovery, compounds, compositions, methods and uses are provided for the treatment of flaviviridae, including HCV, that include the administration of an effective amount of val-mCyd or its salt, ester, prodrug or derivative, optionally in a pharmaceutically acceptable carrier. In an alternative embodiment, val-mCyd is used to treat any virus that replicates through an RNA-dependent RNA polymerase.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L41 ANSWER 36 OF 36 USPATFULL on STN
ACCESSION NUMBER: 2004:88901 USPATFULL
TITLE: 2', 3'-Dideoxynucleoside analogues for the treatment or prevention of Flaviviridae infections
INVENTOR(S): Schinazi, Raymond F., Decatur, GA, UNITED STATES
Striker, Robert, Madison, WI, UNITED STATES
Shi, Junxing, Duluth, GA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004067877	A1	20040408
APPLICATION INFO.:	US 2003-632875	A1	20030801 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-453715P	20020801 (60)
	US 2002-453716P	20020801 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KING & SPALDING, 191 PEACHTREE STREET, N.E., ATLANTA,

GA, 30303-1763
NUMBER OF CLAIMS: 60
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 2416
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the treatment or prevention of Flaviviridae infections, in particular, hepatitis C virus infection, in a host, and in particular, a human, is provided that includes administering an effective amount of a β-L- or β-D-2',3'-dideoxynucleoside or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable diluent or excipient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> FIL STNGUIDE

FILE 'STNGUIDE' ENTERED AT 12:28:47 ON 13 OCT 2004
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 8, 2004 (20041008/UP).

FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 12:29:24 ON 13 OCT 2004
=> => d que l43
L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/RN
L7 0 SEA FILE=REGISTRY ABB=ON PLU=ON 300832-84-2/CRN
L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON (L6 OR L7)
L16 SEL PLU=ON L8 1- CHEM : 4 TERMS
L17 74 SEA L16
L42 61 DUP REM L17 (13 DUPLICATES REMOVED)
L43 4 SEA L42 AND ?CRYST?

=>

=> d ibib abs hit l43
YOU HAVE REQUESTED DATA FROM FILE 'EMBASE' - CONTINUE? (Y)/N:y

L43 ANSWER 1 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003468113 EMBASE
TITLE: Current therapy and new molecular approaches to antiviral treatment and prevention of hepatitis C.
AUTHOR: Hugle T.; Cerny A.
CORPORATE SOURCE: Dr. A. Cerny, Clinica Medica, Ospedale Civico, CH-6903 Lugano, Switzerland. andreas.cerny@bluewin.ch
SOURCE: Reviews in Medical Virology, (2003) 13/6 (361-371).
Refs: 79
ISSN: 1052-9276 CODEN: RMVIEW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index

038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Current therapeutic options for hepatitis C are limited, especially for genotype 1. For genotypes 2 and 3, pegylated interferon in combination with ribavirin, can lead to a sustained virological response in up to 80% of patients. Unfortunately, adverse effects of IFN and ribavirin are a major problem and the list of contraindications for HCV therapy is long, including decompensated cirrhosis of the liver and psychiatric disorders. Therefore, alternative therapeutic approaches are needed. New delivery options for IFN and ribavirin are aimed at optimising efficiency and reducing adverse effects. Recent progress in the molecular virology of HCV has identified new targets for antiviral intervention. Inhibition of HCV gene expression and replication as well as immunotherapeutic concepts aimed at enhancing the cellular immune response against HCV are being explored. Solution of the **crystal** structures of HCV key enzymes led to the design of specific inhibitors including compounds active against the well characterised NS3 serine protease and RNA-dependent RNA polymerase which are currently in the early phase clinical investigation. New strategies for inhibiting HCV gene expression include the use of antisense oligodeoxynucleotides and ribozymes. Immunomodulation by agents such as inosine monophosphate dehydrogenase inhibitors, thymosin-alpha 1, histamine or amantadine are being studied in combination with IFN and/or ribavirin. Immunotherapeutic vaccination with recombinant HCV E1 protein improved host immunity against HCV and thus seems to be a promising new option. Copyright .COPYRGT. 2003 John Wiley & Sons, Ltd.

AB Current therapeutic options for hepatitis C are limited, especially for genotype 1. For genotypes 2 and 3, pegylated interferon in combination with ribavirin, can lead to a sustained virological response in up to 80% of patients. Unfortunately, adverse effects of IFN and ribavirin are a major problem and the list of contraindications for HCV therapy is long, including decompensated cirrhosis of the liver and psychiatric disorders. Therefore, alternative therapeutic approaches are needed. New delivery options for IFN and ribavirin are aimed at optimising efficiency and reducing adverse effects. Recent progress in the molecular virology of HCV has identified new targets for antiviral intervention. Inhibition of HCV gene expression and replication as well as immunotherapeutic concepts aimed at enhancing the cellular immune response against HCV are being explored. Solution of the **crystal** structures of HCV key enzymes led to the design of specific inhibitors including compounds active against the well characterised NS3 serine protease and RNA-dependent RNA polymerase which are currently in the early phase clinical investigation. New strategies for inhibiting HCV gene expression include the use of antisense oligodeoxynucleotides and ribozymes. Immunomodulation by agents such as inosine monophosphate dehydrogenase inhibitors, thymosin-alpha 1, histamine or amantadine are being studied in combination with IFN and/or ribavirin. Immunotherapeutic vaccination with recombinant HCV E1 protein improved host immunity against HCV and thus seems to be a promising new option. Copyright .COPYRGT. 2003 John Wiley & Sons, Ltd.

CT Medical Descriptors:
*hepatitis C: DT, drug therapy
*hepatitis C: ET, etiology
*hepatitis C: PC, prevention
*infection prevention
virus gene
genotype
drug response
drug contraindication
drug delivery system

side effect: SI, side effect
gene expression
drug targeting
immunotherapy
enzyme structure
crystal structure
drug design
drug activity
antiviral activity
protein targeting
immunomodulation
vaccination
Hepatitis C virus
immune response
cellular immunity
hemolytic anemia: SI, side effect
mental disease: SI, side effect
flu like syndrome: SI, side effect
leukopenia: SI, side effect
thrombocytopenia: SI, side effect
teratogenicity
virus replication
drug hypersensitivity: SI, side effect
rash: SI, side effect
human
nonhuman
clinical trial
review
Drug Descriptors:
alpha interferon: AE, adverse drug reaction
alpha interferon: CT, clinical trial
alpha interferon: CB, drug combination
alpha interferon: DT, drug therapy
alpha interferon: TO, drug toxicity
alpha interferon: PR, pharmaceutics
alpha interferon: PD, pharmacology
alpha interferon: SC, subcutaneous drug administration
ribavirin: AE, adverse drug reaction
ribavirin: CT, clinical trial
ribavirin: CB, drug combination
ribavirin: CM, drug comparison
ribavirin: DT, drug therapy
ribavirin: PK, pharmacokinetics
ribavirin: PD, pharmacology
ribavirin: PO, oral drug administration
albumin conjugate: PR, pharmaceutics
liposome: PR, pharmaceutics
polyaminoacid: PR, pharmaceutics
polyaminoacid: PO, oral drug administration
ribavirin derivative: AE, adverse drug reaction
ribavirin derivative: CT, clinical trial
ribavirin derivative: CB, drug combination
ribavirin derivative: CM, drug comparison
ribavirin derivative: DT, drug therapy
ribavirin derivative: PD, pharmacology
viramidine: AE, adverse drug reaction
viramidine: CT, clinical trial
viramidine: CB, drug combination
viramidine: CM, drug comparison
viramidine: DT, drug therapy

viramidine: PD, pharmacology
levovirin: AE, adverse drug reaction
levovirin: CT, clinical trial
levovirin: CM, drug comparison
levovirin: DT, drug therapy
levovirin: PD, pharmacology
proteinase inhibitor: AE, adverse drug reaction
proteinase inhibitor: CT, clinical trial
proteinase inhibitor: DO, drug dose
proteinase inhibitor: DT, drug therapy
proteinase inhibitor: PK, pharmacokinetics
proteinase inhibitor: PD, pharmacology
proteinase inhibitor: PO, oral drug administration
biln 2061: AE, adverse drug reaction
biln 2061: CT, clinical trial
biln 2061: DO, drug dose
biln 2061: DT, drug therapy
biln 2061: PK, pharmacokinetics
biln 2061: PD, pharmacology
biln 2061: PO, oral drug administration
vx 950: DT, drug therapy
vx 950: PD, pharmacology
virus protein
protein NS5B
RNA directed DNA polymerase inhibitor: CT, clinical trial
RNA directed DNA polymerase inhibitor: DT, drug therapy
RNA directed DNA polymerase inhibitor: PD, pharmacology
jtk 003: CT, clinical trial
jtk 003: DT, drug therapy
jtk 003: PD, pharmacology
ribozyme: AE, adverse drug reaction
ribozyme: CT, clinical trial
ribozyme: DT, drug therapy
ribozyme: TO, drug toxicity
ribozyme: PD, pharmacology
hepatozyme: AE, adverse drug reaction
hepatozyme: CT, clinical trial
hepatozyme: DT, drug therapy
hepatozyme: TO, drug toxicity
hepatozyme: PD, pharmacology
antisense oligodeoxynucleotide: CT, clinical trial
antisense oligodeoxynucleotide: DT, drug therapy
antisense oligodeoxynucleotide: PD, pharmacology
isis 14803: CT, clinical trial
isis 14803: DT, drug therapy
isis 14803: PD, pharmacology
RNA derivative: DV, drug development
RNA derivative: DT, drug therapy
RNA derivative: PD, pharmacology
small interfering rna: DV, drug development
small interfering rna: DT, drug therapy
small interfering rna: PD, pharmacology
monoclonal antibody: DT, drug therapy
monoclonal antibody: PD, pharmacology
xtl 002: DT, drug therapy
xtl 002: PD, pharmacology
cicavir: DT, drug therapy
cicavir: PD, pharmacology
immunomodulating agent: CB, drug combination
immunomodulating agent: DT, drug therapy

thymosin alpha1: CT, clinical trial
thymosin alpha1: CB, drug combination
thymosin alpha1: DO, drug dose
thymosin alpha1: DT, drug therapy
thymosin alpha1: PD, pharmacology
inosinate dehydrogenase inhibitor: CB, drug combination
inosinate dehydrogenase inhibitor: DT, drug therapy
inosinate dehydrogenase inhibitor: PD, pharmacology
merimepodib: CT, clinical trial
merimepodib: CB, drug combination
merimepodib: DT, drug therapy
merimepodib: PD, pharmacology
unindexed drug
unclassified drug
CN (1) Vx 950; (2) Jtk 003; **Biln 2061**; Isis 14803; Xtl 002

=> d ibib abs hit l43 2-
YOU HAVE REQUESTED DATA FROM FILE 'EMBASE' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):y

L43 ANSWER 2 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003337607 EMBASE
TITLE: Hepatitis C virus NS3 serine protease as a drug discovery target.
AUTHOR: McPhee F.; Yeung K.-S.; Good A.C.; Meanwell N.A.
CORPORATE SOURCE: K.-S. Yeung, B.-Myers Squibb Pharmaceut. Res. I., 5 Research Parkway, Wallingford, CT 06492, United States. kapsun.yeung@bms.com
SOURCE: Drugs of the Future, (1 May 2003) 28/5 (465-488).
Refs: 196
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Hepatitis C virus NS3 serine protease (HCV Pr) is an extensively studied enzyme for drug intervention. The target presented serious challenges in early screening efforts, however, with the lack of prominent active site features rendering traditional nonpeptidic serine protease inhibitor motifs and high-throughput screening campaigns ineffectual. In contrast, the peptidomimetic structure-based design approach has proven successful in the discovery of potent inhibitors of HCV Pr. Subsequent rational design efforts have led to the identification of an inhibitor that demonstrates efficacy in man, validating the years of research. This review summarizes why HCV Pr provides a viable drug discovery target despite the many obstacles, and details the breakthroughs in protein production and assay development that have facilitated inhibitor advances. The latest inhibitors in preclinical and clinical research and development are also presented, along with a discussion of how the recent HCV Pr clinical candidate challenges much of the dogma surrounding peptidomimetic design. In addition, future issues such as resistance, genotype coverage and HIV-HCV coinfected individuals are considered.
CT Medical Descriptors:

*drug targeting
*Hepatitis C virus
drug screening
enzyme active site
drug efficacy
protein analysis
inhibition kinetics
drug research
drug design
genotype
drug structure
structure activity relation
in vitro study
enzyme structure
enzyme analysis
drug protein binding
binding kinetics
binding affinity
protein motif
nuclear magnetic resonance
protein expression
molecular weight
protein modification
protein degradation
X ray crystallography
crystal structure
enzyme conformation
sequence homology
human
nonhuman
clinical trial
review
Drug Descriptors:
*serine proteinase
*virus protein: EC, endogenous compound
*NS3 protein: EC, endogenous compound
serine proteinase inhibitor: CT, clinical trial
serine proteinase inhibitor: AN, drug analysis
serine proteinase inhibitor: PD, pharmacology
proteinase inhibitor: CT, clinical trial
proteinase inhibitor: AN, drug analysis
proteinase inhibitor: PD, pharmacology
antivirus agent: CT, clinical trial
antivirus agent: AN, drug analysis
antivirus agent: PD, pharmacology
biln 2061: CT, clinical trial
biln 2061: AN, drug analysis
biln 2061: PD, pharmacology
wo 0248172: AN, drug analysis
wo 0248172: DV, drug development
wo 0208244: AN, drug analysis
wo 0208244: DV, drug development
wo 0208198: AN, drug analysis
wo 0208198: DV, drug development
wo 0181325: AN, drug analysis
wo 0181325: DV, drug development
wo 0208187: AN, drug analysis
wo 0208187: DV, drug development
wo 0177113: AN, drug analysis
wo 0177113: DV, drug development

wo 0218369: AN, drug analysis
wo 0218369: DV, drug development
wo 03006490: AN, drug analysis
wo 03006490: DV, drug development
wo 0174768: AN, drug analysis
wo 0174768: DV, drug development
leukocyte elastase inhibitor: AN, drug analysis
leukocyte elastase inhibitor: DV, drug development
leukocyte elastase inhibitor: PK, pharmacokinetics
leukocyte elastase inhibitor: PO, oral drug administration
tryptase inhibitor: AN, drug analysis
tryptase inhibitor: DV, drug development
apc 6336: AN, drug analysis
apc 6336: DV, drug development
cra 6336: AN, drug analysis
cra 6336: DV, drug development
imidazole derivative: AN, drug analysis
imidazole derivative: DV, drug development
unclassified drug

CN (1) Wo 0248172; (2) Wo 0208244; (3) Wo 0208198; (4) Wo 0181325; (5) Wo 0208187; (6) Wo 0177113; (7) Wo 0218369; (8) Wo 03006490; (9) Wo 0174768; **Biln 2061**; Apc 6336; Cra 6336

L43 ANSWER 3 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003318276 EMBASE
TITLE: Promising candidates for the treatment of chronic hepatitis C.
AUTHOR: Walker M.P.; Yao N.; Hong Z.
CORPORATE SOURCE: Z. Hong, Drug Discovery, Ribapharm Inc., 3300 Hyland Avenue, Costa Mesa, CA 92626, United States
SOURCE: Expert Opinion on Investigational Drugs, (1 Aug 2003) 12/8 (1269-1280).
Refs: 113
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global pandemic of chronic liver disease. Current pegylated IFN-α/ribavirin combination therapies are merely 54 - 56% efficacious and are often poorly tolerated. Popular strategies to improve upon existing therapies include efforts to decrease the dosing regime, improve the safety profile and specifically target the liver, the site of HCV replication. A clear goal of novel therapies is to significantly improve the therapeutic response for HCV-infected patients. One popular scheme to accomplish this is to directly target the viral enzymes involved in HCV RNA replication. While peptidomimetics have been pursued as potent and specific inhibitors of the serine protease, nucleoside analogues and non-nucleoside small molecules have been explored as RNA-dependent RNA polymerase inhibitors with promising potential. Advances in the understanding of HCV replication at the molecular level that stem from the use of the subgenomic replicon system, in vitro enzyme assays and from co-

crystallographic structure solutions of the replication enzymes with novel inhibitors have propelled these compounds into clinical development. As these candidates are developed further, there is great hope for a cure for all those chronically infected with HCV.

AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global pandemic of chronic liver disease. Current pegylated IFN-α/ribavirin combination therapies are merely 54 - 56% efficacious and are often poorly tolerated. Popular strategies to improve upon existing therapies include efforts to decrease the dosing regime, improve the safety profile and specifically target the liver, the site of HCV replication. A clear goal of novel therapies is to significantly improve the therapeutic response for HCV-infected patients. One popular scheme to accomplish this is to directly target the viral enzymes involved in HCV RNA replication. While peptidomimetics have been pursued as potent and specific inhibitors of the serine protease, nucleoside analogues and non-nucleoside small molecules have been explored as RNA-dependent RNA polymerase inhibitors with promising potential. Advances in the understanding of HCV replication at the molecular level that stem from the use of the subgenomic replicon system, in vitro enzyme assays and from co-**crystallographic** structure solutions of the replication enzymes with novel inhibitors have propelled these compounds into clinical development. As these candidates are developed further, there is great hope for a cure for all those chronically infected with HCV.

CT Medical Descriptors:
*hepatitis C: DT, drug therapy
*hepatitis C: ET, etiology
Hepatitis C virus
chronic liver disease: DT, drug therapy
chronic liver disease: ET, etiology
drug efficacy
drug tolerability
dose response
drug safety
drug targeting
virus replication
drug response
RNA replication
molecular mechanics
replicon
in vitro study
enzyme assay
crystallography
crystal structure
monotherapy
drug approval
food and drug administration
drug absorption
drug clearance
drug half life
drug structure
antiviral activity
drug distribution
cytokine release
cytokine production
hemolytic anemia
fatigue: SI, side effect
depression: SI, side effect
skin manifestation: SI, side effect
human
nonhuman

review
Drug Descriptors:
*antivirus agent: AE, adverse drug reaction
*antivirus agent: AN, drug analysis
*antivirus agent: DV, drug development
*antivirus agent: DO, drug dose
*antivirus agent: DT, drug therapy
*antivirus agent: TO, drug toxicity
*antivirus agent: PD, pharmacology
*antivirus agent: PO, oral drug administration
*antivirus agent: SC, subcutaneous drug administration
alpha interferon: CB, drug combination
alpha interferon: DT, drug therapy
alpha interferon: PK, pharmacokinetics
ribavirin: CB, drug combination
ribavirin: DT, drug therapy
virus enzyme: EC, endogenous compound
virus RNA: EC, endogenous compound
peptide derivative: AE, adverse drug reaction
peptide derivative: AN, drug analysis
peptide derivative: CB, drug combination
peptide derivative: DV, drug development
peptide derivative: DT, drug therapy
peptide derivative: PD, pharmacology
peptide derivative: SC, subcutaneous drug administration
serine proteinase inhibitor: AN, drug analysis
serine proteinase inhibitor: DV, drug development
serine proteinase inhibitor: DT, drug therapy
serine proteinase inhibitor: PD, pharmacology
serine proteinase inhibitor: PO, oral drug administration
biln 2061: AN, drug analysis
biln 2061: DV, drug development
biln 2061: DT, drug therapy
biln 2061: PD, pharmacology
biln 2061: PO, oral drug administration
nucleoside analog: DV, drug development
nucleoside analog: DT, drug therapy
nucleoside analog: PD, pharmacology
RNA directed DNA polymerase inhibitor: AN, drug analysis
RNA directed DNA polymerase inhibitor: DV, drug development
RNA directed DNA polymerase inhibitor: DT, drug therapy
RNA directed DNA polymerase inhibitor: PD, pharmacology
nm 283: AN, drug analysis
nm 283: DV, drug development
nm 283: DT, drug therapy
nm 283: PD, pharmacology
nm 107: DV, drug development
nm 107: PK, pharmacokinetics
nm 107: PD, pharmacology
enzyme inhibitor: DV, drug development
enzyme inhibitor: DT, drug therapy
enzyme inhibitor: PD, pharmacology
peginterferon alpha2a: CB, drug combination
peginterferon alpha2a: DT, drug therapy
peginterferon alpha2a: PK, pharmacokinetics
recombinant alpha2a interferon: CB, drug combination
recombinant alpha2a interferon: DT, drug therapy
recombinant alpha2a interferon: PK, pharmacokinetics
recombinant alpha2b interferon: CB, drug combination
recombinant alpha2b interferon: DT, drug therapy

recombinant alpha2b interferon: PK, pharmacokinetics
consensus interferon: CB, drug combination
consensus interferon: DT, drug therapy
proteinase inhibitor: DV, drug development
proteinase inhibitor: DT, drug therapy
proteinase inhibitor: PD, pharmacology
thiadiazine derivative: AN, drug analysis
thiadiazine derivative: DV, drug development
thiadiazine derivative: DT, drug therapy
thiadiazine derivative: PD, pharmacology
ribamidine: DV, drug development
ribamidine: DT, drug therapy
ribamidine: TO, drug toxicity
ribamidine: PK, pharmacokinetics
ribamidine: PD, pharmacology
cytokine: EC, endogenous compound
interleukin 2: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
hemoglobin: EC, endogenous compound
thymosin alpha1: AE, adverse drug reaction
thymosin alpha1: CB, drug combination
thymosin alpha1: DV, drug development
thymosin alpha1: DT, drug therapy
thymosin alpha1: PD, pharmacology
thymosin alpha1: SC, subcutaneous drug administration
interleukin 4: EC, endogenous compound
major histocompatibility antigen class 1: EC, endogenous compound
alpha interferon derivative: AE, adverse drug reaction
alpha interferon derivative: DV, drug development
alpha interferon derivative: DT, drug therapy
alpha interferon derivative: PK, pharmacokinetics
alpha interferon derivative: PD, pharmacology
albuferon: AE, adverse drug reaction
albuferon: DV, drug development
albuferon: DT, drug therapy
albuferon: PK, pharmacokinetics
albuferon: PD, pharmacology
unindexed drug
unclassified drug

CN **(1) Biln 2061**; (2) Nm 283; (3) Albuferon; Roferon a; Ro 25 3036; Nm 107

L43 ANSWER 4 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003195244 EMBASE
TITLE: Hepatitis C virus therapies: Current treatments, targets and future perspectives.
AUTHOR: Walker M.P.; Appleby T.C.; Zhong W.; Lau J.Y.N.; Hong Z.
CORPORATE SOURCE: Z. Hong, Ribapharm Inc., Hyland Avenue, Costa Mesa, CA, United States. zhihong@ribapharm.com
SOURCE: Antiviral Chemistry and Chemotherapy, (2003) 14/1 (1-21). Refs: 208
ISSN: 0956-3202 CODEN: ACCHEH
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global epidemic of chronic liver disease. Current combination therapies are at best 80% efficacious and are often poorly tolerated. Strategies to improve the therapeutic response include the development of novel interferons, nucleoside analogues with reduced haemolysis compared with ribavirin and inosine 5'-monophosphate dehydrogenase inhibitors. Compounds in preclinical or early clinical trials include small molecules that inhibit virus-specific enzymes (such as the serine proteases, RNA polymerase and helicase) or interfere with translation (including antisense molecules, iRNA and ribozymes). Advances in understanding HCV replication, obtaining a sub-genomic replicon and contriving potential small animal models, in addition to solving **crystallographic** structures for the replication enzymes, have improved prospects for developing novel therapies. This review summarizes current and evolving treatments for chronic hepatitis C infection. In addition, progress in HCV targets and drug discovery tools valuable in the search for novel anti-HCV agents is detailed.

AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global epidemic of chronic liver disease. Current combination therapies are at best 80% efficacious and are often poorly tolerated. Strategies to improve the therapeutic response include the development of novel interferons, nucleoside analogues with reduced haemolysis compared with ribavirin and inosine 5'-monophosphate dehydrogenase inhibitors. Compounds in preclinical or early clinical trials include small molecules that inhibit virus-specific enzymes (such as the serine proteases, RNA polymerase and helicase) or interfere with translation (including antisense molecules, iRNA and ribozymes). Advances in understanding HCV replication, obtaining a sub-genomic replicon and contriving potential small animal models, in addition to solving **crystallographic** structures for the replication enzymes, have improved prospects for developing novel therapies. This review summarizes current and evolving treatments for chronic hepatitis C infection. In addition, progress in HCV targets and drug discovery tools valuable in the search for novel anti-HCV agents is detailed.

CT Medical Descriptors:
*hepatitis C: DT, drug therapy
*hepatitis C: EP, epidemiology
*hepatitis C: ET, etiology
*chronic liver disease: ET, etiology
drug efficacy
drug tolerance
hemolytic anemia: SI, side effect
side effect: SI, side effect
alanine aminotransferase blood level
virus replication
replicon
crystal structure
RNA translation
untranslated region
internal ribosome entry site
monotherapy
virus load
treatment outcome
treatment indication
immunomodulation
drug safety
treatment failure
chimpanzee

transgenic mouse
Hepatitis GB virus B
IC 50
structure activity relation
drug structure
virus assembly
human
nonhuman
clinical trial
review
priority journal
Drug Descriptors:
*antivirus agent: AE, adverse drug reaction
*antivirus agent: CT, clinical trial
*antivirus agent: AN, drug analysis
*antivirus agent: CB, drug combination
*antivirus agent: CM, drug comparison
*antivirus agent: DV, drug development
*antivirus agent: DO, drug dose
*antivirus agent: DT, drug therapy
*antivirus agent: PD, pharmacology
*antivirus agent: IV, intravenous drug administration
*antivirus agent: SC, subcutaneous drug administration
alpha interferon: AE, adverse drug reaction
alpha interferon: CB, drug combination
alpha interferon: CM, drug comparison
alpha interferon: DO, drug dose
alpha interferon: DT, drug therapy
alpha interferon: PD, pharmacology
nucleoside derivative: AN, drug analysis
nucleoside derivative: CM, drug comparison
nucleoside derivative: DV, drug development
nucleoside derivative: PR, pharmaceutics
nucleoside derivative: PD, pharmacology
ribavirin: AE, adverse drug reaction
ribavirin: CT, clinical trial
ribavirin: CB, drug combination
ribavirin: CM, drug comparison
ribavirin: DO, drug dose
ribavirin: DT, drug therapy
ribavirin: PD, pharmacology
inosinate dehydrogenase inhibitor: CM, drug comparison
inosinate dehydrogenase inhibitor: DT, drug therapy
inosinate dehydrogenase inhibitor: PD, pharmacology
serine proteinase: EC, endogenous compound
RNA polymerase: EC, endogenous compound
helicase: EC, endogenous compound
ribozyme: EC, endogenous compound
recombinant alpha2a interferon: CM, drug comparison
recombinant alpha2a interferon: DO, drug dose
recombinant alpha2a interferon: DT, drug therapy
recombinant alpha2a interferon: PD, pharmacology
recombinant alpha2a interferon: SC, subcutaneous drug administration
recombinant alpha2b interferon: CM, drug comparison
recombinant alpha2b interferon: DO, drug dose
recombinant alpha2b interferon: DT, drug therapy
recombinant alpha2b interferon: PD, pharmacology
recombinant alpha2b interferon: SC, subcutaneous drug administration
consensus interferon: CM, drug comparison
consensus interferon: DO, drug dose

consensus interferon: DT, drug therapy
consensus interferon: PD, pharmacology
consensus interferon: SC, subcutaneous drug administration
peginterferon alpha2b: CT, clinical trial
peginterferon alpha2b: CB, drug combination
peginterferon alpha2b: CM, drug comparison
peginterferon alpha2b: DO, drug dose
peginterferon alpha2b: DT, drug therapy
peginterferon alpha2b: PD, pharmacology
peginterferon alpha2a: CT, clinical trial
peginterferon alpha2a: CB, drug combination
peginterferon alpha2a: CM, drug comparison
peginterferon alpha2a: DO, drug dose
peginterferon alpha2a: DT, drug therapy
peginterferon alpha2a: PD, pharmacology
levovirin: CT, clinical trial
levovirin: AN, drug analysis
levovirin: CM, drug comparison
levovirin: DV, drug development
levovirin: DO, drug dose
levovirin: DT, drug therapy
levovirin: PD, pharmacology
viramidine: CT, clinical trial
viramidine: AN, drug analysis
viramidine: CM, drug comparison
viramidine: DV, drug development
viramidine: DO, drug dose
viramidine: DT, drug therapy
viramidine: PD, pharmacology
merimepodib: CT, clinical trial
merimepodib: AN, drug analysis
merimepodib: CB, drug combination
merimepodib: CM, drug comparison
merimepodib: DV, drug development
merimepodib: DT, drug therapy
merimepodib: PD, pharmacology
thymosin alpha1: CT, clinical trial
thymosin alpha1: AN, drug analysis
thymosin alpha1: CB, drug combination
thymosin alpha1: DV, drug development
thymosin alpha1: DO, drug dose
thymosin alpha1: DT, drug therapy
thymosin alpha1: PD, pharmacology
thymosin alpha1: SC, subcutaneous drug administration
amantadine: CT, clinical trial
amantadine: AN, drug analysis
amantadine: CB, drug combination
amantadine: CM, drug comparison
amantadine: DV, drug development
amantadine: PD, pharmacology
recombinant interleukin 12: CT, clinical trial
recombinant interleukin 12: AN, drug analysis
recombinant interleukin 12: CB, drug combination
recombinant interleukin 12: CM, drug comparison
recombinant interleukin 12: DV, drug development
recombinant interleukin 12: DO, drug dose
recombinant interleukin 12: DT, drug therapy
recombinant interleukin 12: PD, pharmacology
histamine: CT, clinical trial
histamine: AN, drug analysis

histamine: CB, drug combination
histamine: DV, drug development
histamine: DT, drug therapy
histamine: PD, pharmacology
gamma interferon: CT, clinical trial
gamma interferon: AN, drug analysis
gamma interferon: CB, drug combination
gamma interferon: DV, drug development
gamma interferon: DT, drug therapy
gamma interferon: PD, pharmacology
proteinase inhibitor: CT, clinical trial
proteinase inhibitor: DO, drug dose
proteinase inhibitor: PD, pharmacology
proteinase inhibitor: PO, oral drug administration
biln 2061: CT, clinical trial
biln 2061: DO, drug dose
biln 2061: PD, pharmacology
biln 2061: PO, oral drug administration
peptide derivative: AN, drug analysis
peptide derivative: DV, drug development
peptide derivative: PD, pharmacology
peptide alpha keto acid: AN, drug analysis
peptide alpha keto acid: DV, drug development
peptide alpha keto acid: PD, pharmacology
pyrrolidine derivative: AN, drug analysis
pyrrolidine derivative: DV, drug development
pyrrolidine derivative: PD, pharmacology
pyrrolidine 5,5 lactam: AN, drug analysis
pyrrolidine 5,5 lactam: DV, drug development
pyrrolidine 5,5 lactam: PD, pharmacology
IDdb3: DV, drug development
IDdb3: PD, pharmacology
unindexed drug
unclassified drug
isis 14803
gw 3112
gw 2549
gw 0569
n [4 [[[6,7 dihydro 2 (4 methylphenyl) 5h benzocyclohepten 8 yl]carbonyl]amino]benzyl] n,n dimethyl 2h tetrahydropyran 4 aminium chloride
1,1' [1,4 phenylenebis(methylene)]bis(1,4,8,11 tetraazacyclotetradecane)
CN (1) Vx 497; (2) Ceplene; **(3) Biln 2061**; (4) Isis 14803; Zadaxin; Gw 3112; Gw 2549; Gw 0569; Tak 779; Amd 3100; IDdb3

=>.FIL STNGUIDE

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 8, 2004 (20041008/UP).

=>

(FILE 'CONFSCI, MEDICONF, PASCAL, CABA' ENTERED AT 12:35:08 ON 13 OCT 2004)

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=> d que l46
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/RN
L7             0 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/CRN
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L6 OR L7)
L44              SEL  PLU=ON  L8 1- CHEM :       4 TERMS
L45            4 SEA L44
L46            4 DUP REM L45 (0 DUPLICATES REMOVED)


=> d ibib abs l46 1-
YOU HAVE REQUESTED DATA FROM FILE 'PASCAL' - CONTINUE? (Y)/N:y


YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y/(N):y

L46   ANSWER 1 OF 4  PASCAL  COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on
      STN
ACCESSION NUMBER:         2004-0392927   PASCAL
COPYRIGHT NOTICE:         Copyright .COPYRGT. 2004 INIST-CNRS. All rights
                          reserved.
TITLE (IN ENGLISH):       Sensitivity of NS3 serine proteases from hepatitis C
                          virus genotypes 2 and 3 to the inhibitor BILN
                          2061
AUTHOR:                   THIBEAULT Diane; BOUSQUET Christiane; GINGRAS Rock;
                          LAGACE Lisette; MAURICE Roger; WHITE Peter W.; LAMARRE
                          Daniel
CORPORATE SOURCE:         Department of Biological Sciences, Boehringer
                          Ingelheim (Canada) Ltd., Research and Development,
                          Laval, Quebec H7S 2G5, Canada
SOURCE:                   Journal of virology, (2004), 78(14), 7352-7359, 33
                          refs.
                          ISSN: 0022-538X
DOCUMENT TYPE:            Journal
BIBLIOGRAPHIC LEVEL:      Analytic
COUNTRY:                  United States
LANGUAGE:                 English
AVAILABILITY:             INIST-13592, 354000113683220070
AN    2004-0392927   PASCAL
CP    Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
AB    Hepatitis C virus (HCV) displays a high degree of genetic variability.
      Six genotypes and more than 50 subtypes have been identified to date. In
      this report, kinetic profiles were determined for NS3 proteases of
      genotypes la, 1b, 2ac, 2b, and 3a, revealing no major differences in
      activity. In vitro sensitivity studies with BILN 2061
      showed a decrease in affinity for proteases of genotypes 2 and 3
      (K.sub.i, 80 to 90 nM) compared to genotype 1 enzymes (K.sub.i, 1.5 nM).
      To understand the reduced sensitivity of genotypes 2 and 3 to
      BILN 2061, active-site residues in the proximity of the
      inhibitor binding site were replaced in the genotype-1b enzyme with the
      corresponding genotype-2b or -3a residues. The replacement of five
      residues at positions 78, 79, 80, 122, and 132 accounted for most of the
      reduced sensitivity of genotype 2b, while replacement of residue 168
      alone could account for the reduced sensitivity of genotype 3a.
      BILN 2061 remains a potent inhibitor of these
      non-genotype-1 NS3-NS4A proteins, with K.sub.i values below 100 nM. This
      in vitro potency, in conjunction with the good pharmacokinetic data
      reported for humans, suggests that there is potential for BILN
      2061 as an antiviral agent for individuals infected with
```

non-genotype-1 HCV.

L46 ANSWER 2 OF 4 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004-0323488 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Mutations conferring resistance to a potent hepatitis C virus serine protease inhibitor in vitro
AUTHOR: LU Liangjun; PILOT-MATIAS Tami J.; STEWART Kent D.; RANDOLPH John T.; PITHAWALLA Ron; WENPING HE; HUANG Peggy P.; KLEIN Larry L.; MO Hongmei; MOLLA Akhteruzzaman
CORPORATE SOURCE: Antiviral Research,, Abbott Laboratories, Global Pharmaceutical Research and Development, Abbott Park, Illinois, United States; Structural Biology, Abbott Laboratories; Global Pharmaceutical Research and Development, Abbott Park, Illinois, United States
SOURCE: Antimicrobial agents and chemotherapy, (2004), 48(6), 2260-2266, 32 refs.
ISSN: 0066-4804 CODEN: AACHAX
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-13334, 354000112018870510
AN 2004-0323488 PASCAL
CP Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
AB **BILN 2061** is a novel, specific hepatitis C virus (HCV) NS3 serine protease inhibitor discovered by Boehringer Ingelheim that has shown potent activity against HCV replicons in tissue culture and is currently under clinical investigation for the treatment of HCV infection. The poor fidelity of the HCV RNA-dependent RNA polymerase will likely lead to the development of drug-resistant viruses in treated patients. The development of resistance to **BILN 2061** was studied by the in vitro passage of HCV genotype 1b replicon cells in the presence of a fixed concentration of the drug. Three weeks posttreatment, four colonies were expanded for genotypic and phenotypic characterization. The 50% inhibitory concentrations of **BILN 2061** for these colonies were 72- to 1,228-fold higher than that for the wild-type replicon. Sequencing of the individual colonies identified several mutations in the NS3 serine protease gene. Molecular clones containing the single amino acid substitution A156T, R155Q, or D168V resulted in 357-fold, 24-fold, and 144-fold reductions in susceptibility to **BILN 2061**, respectively, compared to the level of susceptibility shown by the wild-type replicon. Modeling studies indicate that all three of these residues are located in close proximity to the inhibitor binding site. These findings, in addition to the three-dimensional structure analysis of the NS3/NS4A serine protease inhibitor complex, provide a strategic guide for the development of next-generation inhibitors of HCV NS3/NS4A serine protease.

L46 ANSWER 3 OF 4 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004-0488805 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of **BILN**

2061

AUTHOR: LLINAS-BRUNET Montse; BAILEY Murray D.; BOLGER Gordon; BROCHU Christian; FAUCHER Anne-Marie; FERLAND Jean Marie; GARNEAU Michel; GHIRO Elise; GORYS Vida; GRAND-MAITRE Chantal; HALMOS Ted; LAPEYRE-PAQUETTE Nicole; LIARD Francine; POIRIER Martin; RHEAUME Manon; TSANTRIZOS Youla S.; LAMARRE Daniel

CORPORATE SOURCE: Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., 2100 Cunard Street, Laval, Quebec H7S 2G5, Canada; Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., 2100 Cunard Street, Laval, Quebec H7S 2G5, Canada

SOURCE: Journal of medicinal chemistry : (Print), (2004), 47(7), 1605-1608
ISSN: 0022-2623 CODEN: JMCMAR

DOCUMENT TYPE: Journal; Letter
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
NOTE: 3/4 p. ref. et notes
AVAILABILITY: INIST-9165, 354000113547020040
AN 2004-0488805 PASCAL
CP Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
AB From the discovery of competitive hexapeptide inhibitors, potent and selective HCV NS3 protease macrocyclic inhibitors have been identified. Structure-activity relationship studies were performed focusing on optimizing the N-terminal carbamate and the aromatic substituent on the (4R)-hydroxyproline moiety. Inhibitors meeting the potency criteria in the cell-based assay and with improved oral bioavailability in rats were identified. **BILN 2061** was selected as the best compound, the first NS3 protease inhibitor reported with antiviral activity in man.

L46 ANSWER 4 OF 4 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004-0112784 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus
AUTHOR: LAMARRE Daniel; ANDERSON Paul C.; BAILEY Murray; BEAULIEU Pierre; BOLGER Cordon; BONNEAU Pierre; BOES Michael; CAMERON Dale R.; CARTIER Mireille; CORDINGLEY Michael G.; FAUCHER Anne-Marie; GOUDREAU Nathalie; KAWAL Stephen H.; KUKOLJ George; LAGACE Lisette; LAPLANTE Steven R.; NARJES Hans; POUPART Marc-Andre; RANCOURT Jean; SENTJENS Roel E.; GEORGE Roger St.; SIMONEAU Bruno; STEINMANN Gerhard; THIBEAULT Diane; TSANTRIZOS Youla S.; WELDON Steven M.; YONG Chan-Lol; LLINAS-BRUNET Montse

CORPORATE SOURCE: Departments of Biological Sciences, Laval, Quebec, H7S 2G5, Canada; Chemistry, Research and Development, Boehringer Ingelheim (Canada) Ltd, Laval, Quebec, H7S 2G5, Canada; Clinical Research, Boehringer Ingelheim Pharma KG, Biberach 88397, Germany, Federal Republic of; Academisch Medisch Center, 1105 AZ, Amsterdam, Netherlands; Research and Development, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut 06877-0368, United States

SOURCE: Nature : (London), (2003), 426(6963), 186-189, 30

refs.
ISSN: 0028-0836 CODEN: NATUAS
DOCUMENT TYPE: Journal; (letter to editor)
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-142, 354000119799120240
AN 2004-0112784 PASCAL

AB Hepatitis C virus (HCV) infection is a serious cause of chronic liver disease worldwide with more than 170 million infected individuals at risk of developing significant morbidity and mortality.sup.1.sup.-.sup.3. Current interferon-based therapies.sup.4 are suboptimal especially in patients infected with HCV genotype 1, and they are poorly tolerated, highlighting the unmet medical need for new therapeutics.sup.5.sup.,.sup.6. The HCV-encoded NS3 protease is essential for viral replication.sup.7.sup.,.sup.8and has long been considered an attractive target for therapeutic intervention in HCV-infected patients. Here we identify a class of specific and potent NS3 protease inhibitors and report the evaluation of **BILN 2061**, a small molecule inhibitor biologically available through oral ingestion and the first of its class in human trials. Administration of **BILN 2061** to patients infected with HCV genotype 1 for 2 days resulted in an impressive reduction of HCV RNA plasma levels, and established proof-of-concept in humans for an HCV NS3 protease inhibitor. Our results further illustrate the potential of the viral-enzyme-targeted drug discovery approach for the development of new HCV therapeutics.

=> stnindex
ENTER FILE OR CLUSTER NAMES (NONE):allbib
FILE 'ENCOMPLIT' ACCESS NOT AUTHORIZED
FILE 'ENCOMPLIT2' ACCESS NOT AUTHORIZED
FILE 'ENCOMPPAT' ACCESS NOT AUTHORIZED
FILE 'ENCOMPPAT2' ACCESS NOT AUTHORIZED

INDEX '1MOBILITY, 2MOBILITY, ABI-INFORM, ADISCTI, AEROSPACE, AGRICOLA, ALUMINIUM, ANABSTR, ANTE, APOLLIT, AQUASCI, AQUALINE, AQUIRE, BABS, BIBLIODATA, BIOBUSINESS, BIOCOMMERCE, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, BLLDB, CABA, CANCERLIT, ...'
ENTERED AT 12:39:28 ON 13 OCT 2004

143 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view search error messages that display as 0* with SET DETAIL OFF.

=> s (?ciluprevir? or (biln 2061?) or (biln(1w)2061?)) and ?cryst?

6 FILES HAVE ONE OR MORE ANSWERS, 143 FILES SEARCHED IN STNINDEX

L47 QUE (?CILUPREVIR? OR (BILN 2061?) OR (BILN(1W) 2061?)) AND ?CRYST?

=> d rank
F1 9 PCTFULL
F2 6 USPATFULL
F3 4 EMBASE

```
F4            3   BIOTECHNO
F5            3   SCISEARCH
F6            1*  INVESTEXT

=> fil biotechno scisearch

=> =>

     (FILE 'BIOTECHNO, SCISEARCH' ENTERED AT 12:45:07 ON 13 OCT 2004)

=> d que l51
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/RN
L7             0 SEA FILE=REGISTRY ABB=ON  PLU=ON  300832-84-2/CRN
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L6 OR L7)
L48              SEL  PLU=ON  L8 1- CHEM :       4 TERMS
L49           32 SEA L48
L50           30 DUP REM L49 (2 DUPLICATES REMOVED)
L51            3 SEA L50 (L) ?CRYST?

=> d ibib abs l51 1-
YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):y

L51   ANSWER 1 OF 3  BIOTECHNO  COPYRIGHT 2004 Elsevier Science B.V. on STN
ACCESSION NUMBER:        2003:37413258   BIOTECHNO
TITLE:                   Current therapy and new molecular approaches to
                         antiviral treatment and prevention of hepatitis C
AUTHOR:                  Hugle T.; Cerny A.
CORPORATE SOURCE:        Dr. A. Cerny, Clinica Medica, Ospedale Civico, CH-6903
                         Lugano, Switzerland.
                         E-mail: andreas.cerny@bluewin.ch
SOURCE:                  Reviews in Medical Virology, (2003), 13/6 (361-371),
                         79 reference(s)
                         CODEN: RMVIEW  ISSN: 1052-9276
DOCUMENT TYPE:           Journal; General Review
COUNTRY:                 United Kingdom
LANGUAGE:                English
SUMMARY LANGUAGE:        English
AN    2003:37413258   BIOTECHNO
AB    Current therapeutic options for hepatitis C are limited, especially for
      genotype 1. For genotypes 2 and 3, pegylated interferon in combination
      with ribavirin, can lead to a sustained virological response in up to 80%
      of patients. Unfortunately, adverse effects of IFN and ribavirin are a
      major problem and the list of contraindications for HCV therapy is long,
      including decompensated cirrhosis of the liver and psychiatric disorders.
      Therefore, alternative therapeutic approaches are needed. New delivery
      options for IFN and ribavirin are aimed at optimising efficiency and
      reducing adverse effects. Recent progress in the molecular virology of
      HCV has identified new targets for antiviral intervention. Inhibition of
      HCV gene expression and replication as well as immunotherapeutic concepts
      aimed at enhancing the cellular immune response against HCV are being
      explored. Solution of the crystal structures of HCV key enzymes led to
      the design of specific inhibitors including compounds active against the
      well characterised NS3 serine protease and RNA-dependent RNA polymerase
      which are currently in the early phase clinical investigation. New
      strategies for inhibiting HCV gene expression include the use of
```

antisense oligodeoxynucleotides and ribozymes. Immunomodulation by agents such as inosine monophosphate dehydrogenase inhibitors, thymosin-alpha 1, histamine or amantadine are being studied in combination with IFN and/or ribavirin. Immunotherapeutic vaccination with recombinant HCV E1 protein improved host immunity against HCV and thus seems to be a promising new option. Copyright .COPYRGT. 2003 John Wiley & Sons, Ltd.

L51 ANSWER 2 OF 3 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2003:36949689 BIOTECHNO
TITLE: Promising candidates for the treatment of chronic hepatitis C
AUTHOR: Walker M.P.; Yao N.; Hong Z.
CORPORATE SOURCE: Z. Hong, Drug Discovery, Ribapharm Inc., 3300 Hyland Avenue, Costa Mesa, CA 92626, United States.
SOURCE: Expert Opinion on Investigational Drugs, (01 AUG 2003), 12/8 (1269-1280), 113 reference(s)
CODEN: EOIDER ISSN: 1354-3784
DOCUMENT TYPE: Journal; General Review
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2003:36949689 BIOTECHNO
AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global pandemic of chronic liver disease. Current pegylated IFN-α/ribavirin combination therapies are merely 54 - 56% efficacious and are often poorly tolerated. Popular strategies to improve upon existing therapies include efforts to decrease the dosing regime, improve the safety profile and specifically target the liver, the site of HCV replication. A clear goal of novel therapies is to significantly improve the therapeutic response for HCV-infected patients. One popular scheme to accomplish this is to directly target the viral enzymes involved in HCV RNA replication. While peptidomimetics have been pursued as potent and specific inhibitors of the serine protease, nucleoside analogues and non-nucleoside small molecules have been explored as RNA-dependent RNA polymerase inhibitors with promising potential. Advances in the understanding of HCV replication at the molecular level that stem from the use of the subgenomic replicon system, in vitro enzyme assays and from co-crystallographic structure solutions of the replication enzymes with novel inhibitors have propelled these compounds into clinical development. As these candidates are developed further, there is great hope for a cure for all those chronically infected with HCV.

L51 ANSWER 3 OF 3 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2003:36565908 BIOTECHNO
TITLE: Hepatitis C virus therapies: Current treatments, targets and future perspectives
AUTHOR: Walker M.P.; Appleby T.C.; Zhong W.; Lau J.Y.N.; Hong Z.
CORPORATE SOURCE: Z. Hong, Ribapharm Inc., Hyland Avenue, Costa Mesa, CA, United States.
E-mail: zhihong@ribapharm.com
SOURCE: Antiviral Chemistry and Chemotherapy, (2003), 14/1 (1-21), 208 reference(s)
CODEN: ACCHEH ISSN: 0956-3202
DOCUMENT TYPE: Journal; General Review
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2003:36565908 BIOTECHNO

AB Chronic hepatitis C virus (HCV) infection is the cause of an emerging global epidemic of chronic liver disease. Current combination therapies are at best 80% efficacious and are often poorly tolerated. Strategies to improve the therapeutic response include the development of novel interferons, nucleoside analogues with reduced haemolysis compared with ribavirin and inosine 5'-monophosphate dehydrogenase inhibitors. Compounds in preclinical or early clinical trials include small molecules that inhibit virus-specific enzymes (such as the serine proteases, RNA polymerase and helicase) or interfere with translation (including antisense molecules, iRNA and ribozymes). Advances in understanding HCV replication, obtaining a sub-genomic replicon and contriving potential small animal models, in addition to solving crystallographic structures for the replication enzymes, have improved prospects for developing novel therapies. This review summarizes current and evolving treatments for chronic hepatitis C infection. In addition, progress in HCV targets and drug discovery tools valuable in the search for novel anti-HCV agents is detailed.

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 12:47:48 ON 13 OCT 2004

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 8, 2004 (20041008/UP).

=>

```
=> fil confsci

FILE 'CONFSCI' ENTERED AT 13:26:46 ON 13 OCT 2004
COPYRIGHT (C) 2004 Cambridge Scientific Abstracts (CSA)

FILE COVERS 1973 TO 23 Sep 2004 (20040923/ED)

=> fil mediconf

FILE 'MEDICONF' ENTERED AT 13:26:50 ON 13 OCT 2004
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FILE LAST UPDATED: 27 SEP 2004        <20040927/UP>

=> fil pascal

FILE 'PASCAL' ENTERED AT 13:26:55 ON 13 OCT 2004
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FILE LAST UPDATED: 11 OCT 2004        <20041011/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE
    IN THE BASIC INDEX (/BI) FIELD  <<<

=> fil caba

FILE 'CABA' ENTERED AT 13:26:59 ON 13 OCT 2004
COPYRIGHT (C) 2004 CAB INTERNATIONAL (CABI)

FILE COVERS 1973 TO 3 Sep 2004 (20040903/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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=> fil biotechno

FILE 'BIOTECHNO' ENTERED AT 13:27:07 ON 13 OCT 2004
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FILE LAST UPDATED: 7 JAN 2004        <20040107/UP>
FILE COVERS 1980 TO 2003.

>>>  BIOTECHNO IS NO LONGER BEING UPDATED AS OF 2004  <<<

>>>  SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN
     /CT AND BASIC INDEX  <<<

=> fil scisearch

FILE 'SCISEARCH' ENTERED AT 13:27:12 ON 13 OCT 2004
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FILE COVERS 1974 TO 8 Oct 2004 (20041008/ED)
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```
=> file stnguide

FILE 'STNGUIDE' ENTERED AT 13:27:15 ON 13 OCT 2004
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AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct  8, 2004 (20041008/UP).

=>
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=> fil reg

FILE 'REGISTRY' ENTERED AT 13:32:02 ON 13 OCT 2004
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 11 OCT 2004 HIGHEST RN 760932-70-5
DICTIONARY FILE UPDATES: 11 OCT 2004 HIGHEST RN 760932-70-5

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> fil lreg

FILE 'LREGISTRY' ENTERED AT 13:32:05 ON 13 OCT 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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LREGISTRY IS A STATIC LEARNING FILE

=> fil bei

FILE 'BEILSTEIN' ENTERED AT 13:32:08 ON 13 OCT 2004

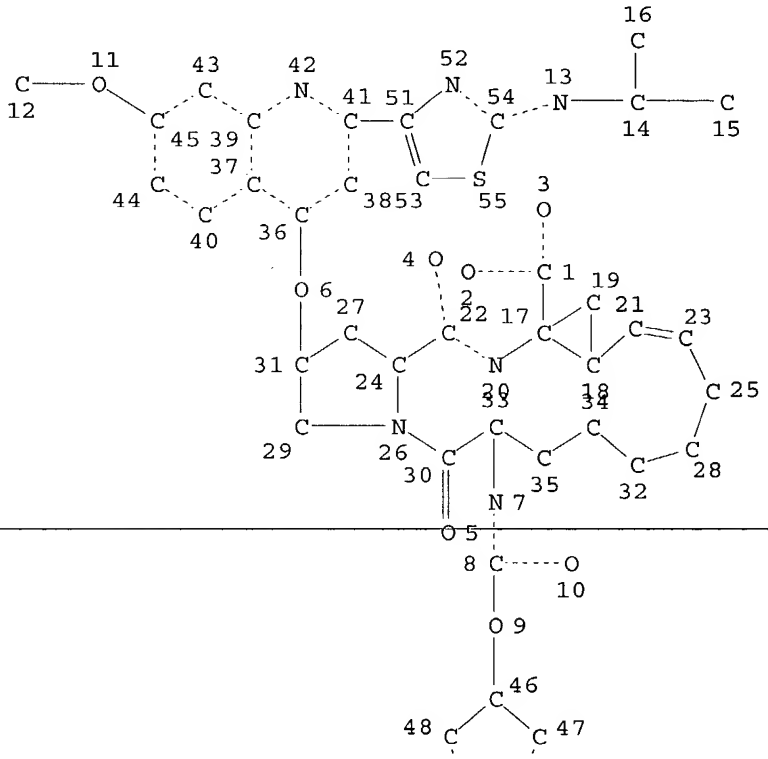
FILE RELOADED ON OCTOBER 20, 2002
FILE LAST UPDATED ON JUNE 15, 2004

FILE COVERS 1771 TO 2003.
*** FILE CONTAINS 8,997,153 SUBSTANCES ***

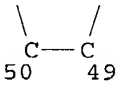
>>>PLEASE NOTE: Reaction Data and substance data are stored in
separate documents and can not be searched together in one query.
Reaction data for BEILSTEIN compounds may be displayed
immediately with the display codes PRE (preparations) and REA
(reactions). A substance answer set retrieved after the search
for a chemical name, a compounds with available reaction
information by combining with PRE/FA, REA/FA or more generally
with RX/FA. The BEILSTEIN Registry Number (BRN) is the link
between a BEILSTEIN compound and belonging reactions. For mo
detailed reaction searches BRNs can be searched as reaction
partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

=> d que l53
L52 STR



Page 1-A



Page 2-A
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 55

STEREO ATTRIBUTES: NONE
L53 0 SEA FILE=BEILSTEIN SSS FUL L52

=>

=> fil zcaplus

FILE 'ZCAPLUS' ENTERED AT 14:36:44 ON 13 OCT 2004
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 13 Oct 2004 VOL 141 ISS 16
FILE LAST UPDATED: 12 Oct 2004 (20041012/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil hcap

FILE 'HCAPLUS' ENTERED AT 14:36:47 ON 13 OCT 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 13 Oct 2004 VOL 141 ISS 16
FILE LAST UPDATED: 12 Oct 2004 (20041012/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil biosis

FILE 'BIOSIS' ENTERED AT 14:36:50 ON 13 OCT 2004

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 6 October 2004 (20041006/ED)

FILE RELOADED: 19 October 2003.

=> fil pascal

FILE 'PASCAL' ENTERED AT 14:36:53 ON 13 OCT 2004

FILE LAST UPDATED: 11 OCT 2004 <20041011/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE
IN THE BASIC INDEX (/BI) FIELD <<<

=> fil confsci

FILE 'CONFSCI' ENTERED AT 14:36:58 ON 13 OCT 2004

FILE COVERS 1973 TO 23 Sep 2004 (20040923/ED)

=> fil caba

FILE 'CABA' ENTERED AT 14:37:01 ON 13 OCT 2004

FILE COVERS 1973 TO 3 Sep 2004 (20040903/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

The CABA file was reloaded 7 December 2003. Enter HELP RLOAD for details.

=> fil medlin

FILE 'MEDLINE' ENTERED AT 14:37:05 ON 13 OCT 2004

FILE LAST UPDATED: 12 OCT 2004 (20041012/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
description of changes.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> fil embas

FILE 'EMBASE' ENTERED AT 14:37:09 ON 13 OCT 2004

FILE COVERS 1974 TO 7 Oct 2004 (20041007/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> file stnguide

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 8, 2004 (20041008/UP).

=>

(FILE 'HCAPLUS, BIOSIS, PASCAL, CONFSCI, CABA, MEDLINE, EMBASE' ENTERED

=> d que l71
L54 15 SEA ("CERRETA M K"/AU OR "CERRETA MICHAEL K"/AU OR "CERRETA MICHAEL KENNETH"/AU)
L55 50 SEA ("VARSOLONA R J"/AU OR "VARSOLONA RICHARD"/AU OR "VARSOLONA RICHARD J"/AU)
L56 1 SEA SMOLIGA,J?/AU
L57 66 SEA (L54 OR L55 OR L56)
L58 45 DUP REM L57 (21 DUPLICATES REMOVED)
L59 429328 SEA HCV OR ?HEPATITI?
L60 0 SEA L58 AND L59
L61 159 SEA ?CILUPREVIR? OR BILN?
L62 0 SEA L58 AND L61
L63 30112 SEA ?BOEHRINGER?
L64 12432 SEA ?INGELHEIM?
L65 0 SEA L58 AND (L63 OR L64)
L66 31742 SEA ?BOEHRINGER?/PA,CS,SO
L67 20390 SEA ?INGELHEIM?/PA,CS,SO
L68 1 SEA L58 AND (L66 OR L67)
L69 24 SEA L58 AND ?CRYST?
L70 25 SEA L60 OR L62 OR L65 OR L68 OR L69
L71 25 SEA L70 OR L56

=> d ibib abs
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, BIOSIS, PASCAL, EMBASE' - CONTINUE?
(Y)/N:y

L71 ANSWER 1 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:877280 HCAPLUS
DOCUMENT NUMBER: 140:111069
TITLE: Scalable, efficient process for the synthesis of (R)-3,5-bistrifluoromethylphenyl ethanol via catalytic asymmetric transfer hydrogenation and isolation as a DABCO inclusion complex
AUTHOR(S): Hansen, Karl B.; Chilenski, Jennifer R.; Desmond, Richard; Devine, Paul N.; Grabowski, Edward J. J.; Heid, Richard; Kubryk, Michele; Mathre, David J.; **Varsolona, Richard**
CORPORATE SOURCE: Merck Research Laboratories, Department of Process

Research, Rahway, NJ, 07065, USA
SOURCE: Tetrahedron: Asymmetry (2003), 14(22), 3581-3587
CODEN: TASYE3; ISSN: 0957-4166
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:111069
AB (R)-3,5-Bistrifluoromethylphenyl ethanol (I), a key building block in the synthesis of aprepitant, has been synthesized from corresponding ketone via catalytic asym. transfer hydrogenation using a simplified catalyst generation procedure. The process uses (1S,2R)-cis-1-aminoindan-2-ol and dichloro(p-cymene)Ru(II)dimer as the chiral ligand and metal source for the reduction While the reduction provides I in 90-92% ee, an isolation of I as a
2:1 inclusion complex with DABCO was developed to allow for the upgrade of the enantiomeric excess to >99%. **Crystal** structure of this complex was also reported.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs 2-
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, BIOSIS, PASCAL, EMBASE' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 24 ANSWERS - CONTINUE? Y/(N):y

L71 ANSWER 2 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:902262 HCAPLUS
DOCUMENT NUMBER: 138:4786
TITLE: Thermodynamically stable **crystal** form of the insecticidal 4''-deoxy-4''-epi-methylamino avermectin B1a/B1b benzoic acid salt, and processes for its preparation
INVENTOR(S): Cvetovich, Raymond; McCauley, James A.; Demchak, Richard; **Varsolona, Richard J.**
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: U.S., 4 pp., Cont.-in-part of U.S. Ser. No. 109,189, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6486195	B1	20021126	US 1995-376318	19950120
CN 1129453	A	19960821	CN 1994-193136	19940815
CN 1041523	B	19990106		
HU 73552	A2	19960828	HU 1996-345	19940815
HU 217769	B	20000428		
BR 9407300	A	19961008	BR 1994-7300	19940815
ES 2139753	T3	20000216	ES 1994-926502	19940815
PT 714400	T	20000531	PT 1994-926502	19940815
CZ 287929	B6	20010314	CZ 1996-459	19940815
ZA 9406203	A	19950331	ZA 1994-6203	19940817
WO 9622300	A1	19960725	WO 1996-US459	19960116

W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS,

JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL,
RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AZ, BY, KG,
KZ, RU
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR,
NE, SN, TD, TG

AU 9646990	A1	19960807	AU 1996-46990	19960116
LV 12571	B	20010420	LV 2000-120	20000907
PRIORITY APPLN. INFO.:			US 1993-109189	B2 19930819
			US 1995-376318	A 19950120
			WO 1996-US459	W 19960116

OTHER SOURCE(S): CASREACT 138:4786

AB The most thermodynamically stable **crystalline** form of the insecticidal benzoic acid salt of 4''-deoxy-4''-epi-methylamino avermectin B1a/B1b as the hemihydrate is obtained by **crystallization** from organic solvents containing a controlled amount of water.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L71 ANSWER 3 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:859280 HCAPLUS
DOCUMENT NUMBER: 139:312088
TITLE: A spectroscopic and **crystallographic** study of polymorphism in an aza-steroid. [Erratum to document cited in CA134:32861]
AUTHOR(S): Wenslow, Robert M.; Baum, Mary W.; Ball, Richard G.; McCauley, James A.; **Varsolona, Richard J.**
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065-0900, USA
SOURCE: Journal of Pharmaceutical Sciences (2002), 91(11), 2465
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The solubility anal. in the exptl. section is incorrect. While the information about solubility trends and form stability are correct, the actual solubility values are unreliable. The solubility measurements portion of the exptl. section (page 1271), Figure 3 (page 1273), and the second paragraph of the results and discussion section (page 1272) must be retracted.

L71 ANSWER 4 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:185054 HCAPLUS
DOCUMENT NUMBER: 136:232164
TITLE: Preparation of the dihydroxy open-acid salt of simvastatin as a HMG-CoA reductase inhibitor for pharmaceutical use in the treatment of conditions, such as hypercholesteremia and atherosclerosis
INVENTOR(S): Tillyer, Richard D.; Reider, Paul J.; Grabaowski, Edward J. J.; Xu, Feng; Wenslow, Robert M.; Vega, Jose M.; **Varsolona, Richard J.**
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002020457	A1	20020314	WO 2001-US27466	20010905
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001088724	A5	20020322	AU 2001-88724	20010905
EP 1324972	A1	20030709	EP 2001-968480	20010905
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004508347	T2	20040318	JP 2002-525082	20010905
US 2003176501	A1	20030918	US 2002-293153	20021113
PRIORITY APPLN. INFO.:			US 2000-656109 A	20000906
			US 2000-660956 A1	20000913
			WO 2001-US27466 W	20010905

AB **Crystalline** forms of open chain simvastatin were prepared for use in pharmaceutical compns. for inhibiting HMG-CoA reductase, as well as for treating and/or reducing the risk for diseases and conditions affected by inhibition of HMG-CoA reductase, comprising orally administering a therapeutically effective amount of a **crystalline** hydrated form of the calcium salt of dihydroxy open acid simvastatin to a patient in need of such treatment. Thus, simvastatin was treated with Ca(OAc)2 and 1N HCl to form open-chain simvastatin acid calcium salt. Pharmacokinetics and HMG-CoA reductase inhibiting activity of the prepared simvastatin derivs. were examined

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L71 ANSWER 5 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:78384 HCAPLUS

DOCUMENT NUMBER: 134:136678

TITLE: **Crystal** forms of 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone

INVENTOR(S): **Varsolona, Richard J.**; McCauley, James A.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

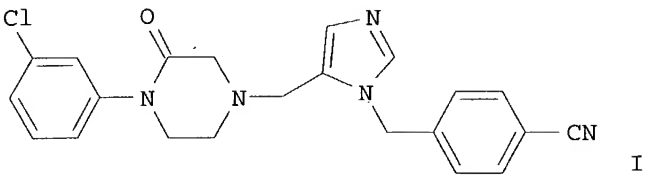
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007437	A1	20010201	WO 2000-US19423	20000717
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 1999-144954P P 19990721
GI



I

AB The present invention is directed to the **crystal** forms of 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone (I), which may inhibit farnesyl-protein transferase, and the process for the preparation of these **crystal** forms. The hydrate and 2 other **crystal** forms of I were prepared and pharmaceutical formulations given.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L71 ANSWER 6 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:737606 HCAPLUS
DOCUMENT NUMBER: 134:32861
TITLE: A spectroscopic and **crystallographic** study of polymorphism in an aza-steroid
AUTHOR(S): Wenslow, Robert M.; Baum, Mary W.; Ball, Richard G.; Mccauley, James A.; **Varsolona, Richard J.**
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065-0900, USA
SOURCE: Journal of Pharmaceutical Sciences (2000), 89(10), 1271-1285
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **crystal** structures of 2 enantiotropic polymorphs of the aza-steroid, finasteride, were determined The solid-state NMR spectra, IR spectra, and phys. property data of these 2 polymorphs are discussed in relation to both their solid-state structures and hydrogen-bonding networks.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L71 ANSWER 7 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:335413 HCAPLUS
DOCUMENT NUMBER: 132:339389
TITLE: Therapeutic polymorphs of a GABA-A α-5 inverse agonist and pamoate formulations
INVENTOR(S): Kaufman, Michael J.; McCauley, James A.; Rush, Daniel J.; Tschaen, David M.; **Varsolona, Richard J.**; Ho, Guo-Jie
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027849	A2	20000518	WO 1999-US26622	19991110
WO 2000027849	A3	20000831		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1129094	A2	20010905	EP 1999-961637	19991110
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002529468	T2	20020910	JP 2000-581027	19991110
US 2001049439	A1	20011206	US 2000-728497	20001130
US 6534505	B2	20030318		

PRIORITY APPLN. INFO.:	US 1998-108007P	P	19981112
	US 1999-437928	A3	19991110
	WO 1999-US26622	W	19991110

AB Pharmaceutical compns. containing 3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl)methoxy-1,2,4-triazolo[3,4-a]phthalazine (I) as a dihydrate, a dehydrate of the dihydrate and a pentahydrate for enhancing cognition, and pamoate are described. I dihydrate (0.99 g) was dry mixed with disodium pamoate (3.6 g), HPC-LF (0.225 g) and Avicel PH-102 (1.155 g) until a uniform mixture was obtained. Small amts. of water (1.75 g) were added and mixed into the powder until granules were obtained. The granules were sieved and permitted to air dry for 7 days. Dried granules (2.43 g) were mixed with PVP (0.0972 g) for 2 min. Ten tablets (nominal weight 208 mg) were compressed from the granulate. The tablets were introduced to 900-g placebo tablets and warmed to 40°, after which a 15% Surerelease dispersion in water was applied until a 10% weight gain was achieved. The resulting enteric coated tablets were stored at RT for future use.

L71 ANSWER 8 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:709087 HCAPLUS
DOCUMENT NUMBER: 129:290373
TITLE: Flowable, nondigestible oil and manufacturing process
INVENTOR(S): **Cerreta, Michael Kenneth**; Lin, Peter Yau-Tak; Edwards, Penelope Marie; Agerton, Mark Lewis
PATENT ASSIGNEE(S): The Procter & Gamble Company, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9847909	A1	19981029	WO 1998-US6708	19980403
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,				

NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9872457	A1	19981113	AU 1998-72457	19980403
EP 977765	A1	20000209	EP 1998-919733	19980403

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI

PRIORITY APPLN. INFO.:	US 1997-844590	19970421
	US 1997-914743	19970819
	WO 1998-US6708	19980403

AB A title oil composition having a consistency of <600 P·sec(n-1) in a temperature range of 20-40° contains a liquid polyol (preferably sucrose) polyester having a complete melt point <37° (body temperature), and a solid polyol polyester having a complete melt point of ≥37° and containing saturated polyol polyester capable of forming **crystallized** spherulites. The composition is flowable at ordinary ambient temperature and also provides good control of passive oil loss (leakage of the liquid nondigested fat through the anal sphincter). The composition is made by melting completely the nondigestible oil containing the solid polyol fatty acid polyester, e.g., sucrose octabehenate, **crystallizing** a portion of the solid polyester into **crystallized** spherulites (cores), further reducing the temperature to an ambient **crystallization** temperature, and holding the polyol polyester composition for a time sufficient to **crystallize** the remaining portion of the solid polyol polyesters diversely esterified, e.g., with C18 (un)saturated fatty acid mixts. around the solid core. The process is accompanied by shearing of the composition during the **crystallization** of the remaining portion of the solid polyol fatty acid polyester. The process is generally completed within 5 h, usually within .apprx.2 h.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L71 ANSWER 9 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	1997:717898 HCAPLUS
DOCUMENT NUMBER:	128:22922
TITLE:	Preparation of 3-amino-2-pyrazinone-1-acetamide derivatives as thrombin inhibitors
INVENTOR(S):	Sanderson, Philip E.; Lyle, Terry A.; Dorsey, Bruce D.; **Varsolona, Richard J.**
PATENT ASSIGNEE(S):	Merck & Co., Inc., USA; Sanderson, Philip E.; Lyle, Terry A.; Dorsey, Bruce D.; Varsolona, Richard J.
SOURCE:	PCT Int. Appl., 193 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9740024	A1	19971030	WO 1997-US6744	19970418

W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

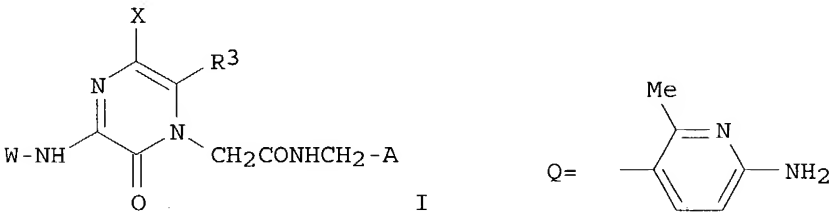
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

CA 2252964	AA	19971030	CA 1997-2252964	19970418

AU 9726799	A1	19971112	AU 1997-26799		19970418
AU 714985	B2	20000113			
EP 900207	A1	19990310	EP 1997-918780		19970418
EP 900207	B1	20011121			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO					
BR 9708859	A	19990803	BR 1997-8859		19970418
NZ 331993	A	20000428	NZ 1997-331993		19970418
JP 2000508334	T2	20000704	JP 1997-538296		19970418
JP 3140790	B2	20010305			
TR 9802133	T2	20000921	TR 1998-9802133		19970418
AT 209191	E	20011215	AT 1997-918780		19970418
ZA 9703437	A	19971023	ZA 1997-3437		19970422
NO 9804928	A	19981222	NO 1998-4928		19981022
KR 2000010650	A	20000225	KR 1998-708609		19981022
PRIORITY APPLN. INFO.:			US 1996-16041P	P	19960423
			GB 1996-9714	A	19960509
			US 1997-43009P	P	19970414
			WO 1997-US6744	W	19970418

OTHER SOURCE(S): MARPAT 128:22922

GI



I

AB Compds. of general formula [I; W = H, R1, R1O2C, R1CO, R1(CH2)nNHCO, (R1)2CH(CH2)nNHCO; wherein n = 1-4; R1 = R2, R2 (CH2)m C(R12)2, R2CH(OR2)(CH2)p, R2C(R12)2(CH2)m, R2CH2C(R12)2(CH2)q, (R2)2CH(CH2)r, R2O(CH2)p, R2(CO2R3)(CH2)s, etc.; wherein p, s = 1-4; m = 0-3; q = 0-2; r = 0-4; R2 = (un)substituted Ph, naphthyl, biphenyl, (un)substituted and (un)saturated 5- to 7-membered mono- or 9- to 10-membered bicyclic heterocyclic ring or non-heterocyclic ring, wherein the heterocyclic ring contains 1-4 heteroatoms selected from N, O, and S; R3 = H, C1-4 alkyl, C3-7 cycloalkyl, CF3; X = H, halo; ring-(un)substituted 2-amino-5-pyridyl or 2-amino-4-pyridyl, (un)substituted Ph] are prepared These compds. are useful in inhibiting thrombin (serine protease) and associated thrombotic occlusions. This invention also includes a pharmaceutical composition containing I for inhibiting thrombus formation and a method for inhibiting thrombin in blood and formation of blood platelet aggregates by adding the composition to the blood and also a method for inhibiting thrombus formation by adding the composition to the blood and/or with a fibrinogen receptor antagonist. A method for treating or preventing venous thromboembolism and pulmonary embolism, deep vein thrombosis, cardiogenic thromboembolism, thromboembolic stroke, thrombus associated with cancer and cancer chemotherapy, unstable angina, myocardial infarction, cardiogenic thromboembolism associated with atrial fibrillation, prosthetic heart valves, or heart disease, atherosclerosis, etc. in a mammal by administering the composition is claimed. Thus, 3-(2-phenethylamino)-6-methyl-1-carboxypyridine was condensed with 2-amino-5-aminomethyl-6-methylpyridine dihydrochloride using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride,

HOBT.H2O, and N-methylmorpholine in DMF for 16 h to give I (W = CH2CH2Ph, X = H, R3 = Me, A = Q) (II). II in vitro inhibited human α-thrombin with Ki of ≤1 nM. A polymorphic **crystalline** form type A and type B monohydrate of II.2HCl were also prepared and claimed. Pharmaceutical compns., e.g. an tablet formulation containing II, were described.

L71 ANSWER 10 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:545815 HCAPLUS
DOCUMENT NUMBER: 127:225180
TITLE: Two methods for the measurement of the dissociation pressure of a **crystalline** hydrate
AUTHOR(S): Crocker, Louis S.; **Varsolona, Richard J.**; Mccauley, James A.
CORPORATE SOURCE: Merck Research Laboratories, Analytical Research Department, Rahway, NJ, 07065, USA
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (1997), 15(11), 1661-1665
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two methods for the measurement of the characteristic dissociation pressures of a system containing water vapor and two different **crystalline** hydrates of the pharmaceutical compound MK-0677 are described. One method involves the spectroscopic determination of water in gases equilibrated with the solids at controlled temps., using an IR spectrometer. The second method utilizes the extrapolated onset temperature of the transition from one hydrate to the other at controlled humidities, as observed by differential scanning calorimetry. The methods give similar results for the system of interest.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L71 ANSWER 11 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:513504 HCAPLUS
DOCUMENT NUMBER: 127:149281
TITLE: Process for the production of finasteride polymorphic form I via **crystallization**
INVENTOR(S): McCauley, James A.; **Varsolona, Richard J.**
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: U.S., 6 pp., Cont.-in-part of U.S. 5,468,860.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5652365	A	19970729	US 1995-411685	19950330
US 5468860	A	19951121	US 1993-10734	19930129
WO 9411387	A2	19940526	WO 1993-US10659	19931105
WO 9411387	A3	19940929		
W: BB, BG, BR, BY, CZ, FI, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ				
RW: BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
PL 179379	B1	20000831	PL 1993-309050	19931105
US 5886184	A	19990323	US 1997-824426	19970326
PRIORITY APPLN. INFO.:			US 1992-978535 B2	19921119

US 1993-10734	A2	19930129
WO 1993-US10659	W	19931105
US 1995-411685	A3	19950330

AB Polymorphic form I of finasteride, 17β-(N-tert-Bu carbamoyl)-4-aza-5α-androst-1-en-3-one, is produced in substantially pure form using the steps of: (1) **crystallization** from a solution of finasteride in a water immiscible organic solvent and 0% or more by weight of water, producing solvated and non-solvated finasteride in solution, such that the amount of organic solvent and water in the solution is sufficient to cause the solubility of the non-solvated form of finasteride to be exceeded and the non-solvated form of finasteride to be less soluble than any other form of finasteride in the organic solvent and water solution: (2) recovering the resultant solid phase; and (3) removing the solvent therefrom; wherein the water immiscible organic solvent is Et acetate or iso-Pr acetate and the amount of water in the solvent mixture is below 4 mg./mL.

L71 ANSWER 12 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	1997:394288 HCAPLUS
DOCUMENT NUMBER:	127:5081
TITLE:	Preparation of polymorphic forms of a growth hormone release stimulant
INVENTOR(S):	Draper, Jerome P.; Dubost, David C.; Kaufman, Michael J.; McCauley, James A.; Vandrilla, Jennifer L.; **Varsolona, Richard J.**
PATENT ASSIGNEE(S):	Merck and Co., Inc., USA
SOURCE:	PCT Int. Appl., 85 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9715574	A1	19970501	WO 1996-US16955	19961023
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2235371	AA	19970501	CA 1996-2235371	19961023
AU 9674686	A1	19970515	AU 1996-74686	19961023
AU 707946	B2	19990722		
JP 10512295	T2	19981124	JP 1996-516737	19961023
BR 9611229	A	19990525	BR 1996-11229	19961023
EP 1019402	A1	20000719	EP 1996-936869	19961023
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 3204266	B2	20010904	JP 1997-516737	19961023
ZA 9608989	A	19970429	ZA 1996-8989	19961025
NO 9801867	A	19980629	NO 1998-1867	19980424
HK 1017894	A1	20010928	HK 1999-102961	19990712

PRIORITY APPLN. INFO.:	US 1995-5900P	P	19951027
	GB 1996-3361	A	19960216
	WO 1996-US16955	W	19961023

AB The title stimulant (no data), N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate was

prepared in a multistep synthesis and converted to multiple characterized polymorphic forms. The instant polymorphic forms have advantages over the other known forms in terms of thermodn. stability and suitability for inclusion in pharmaceutical formulations.

L71 ANSWER 13 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:567328 HCAPLUS
DOCUMENT NUMBER: 125:188360
TITLE: Thermodynamically stable **crystal** form of 4"-deoxy-4"-epi-methylamino avermectin b1a/b1b benzoic acid salt and processes for its preparation
INVENTOR(S): Cvetovich, Raymond; Demchak, Richard; Mccauley, James A.; **Varsolona, Richard J.**
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9622300	A1	19960725	WO 1996-US459	19960116
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AZ, BY, KG, KZ, RU				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6486195	B1	20021126	US 1995-376318	19950120
AU 9646990	A1	19960807	AU 1996-46990	19960116
PRIORITY APPLN. INFO.:			US 1995-376318 A	19950120
			US 1993-109189 B2	19930819
			WO 1996-US459 W	19960116

AB The most thermodynamically stable **crystalline** form of the benzoic acid salt of 4"-epi-methylamino avermectin B1a/B1b as the hemihydrate is obtained by **crystallization** from organic solvents containing a controlled amount of water. The obtained product is referred to as **crystal** form B or Type B, and is designated for use as an agricultural insecticide.

L71 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:1006742 HCAPLUS
DOCUMENT NUMBER: 124:117692
TITLE: New finasteride processes
INVENTOR(S): Dolling, Ulf H.; McCauley, James A.; **Varsolona, Richard J.**
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: U.S., 4 pp. Cont.-in-part of U.S. Ser. No. 978,535, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US	5468860	A	19951121	US 1993-10734	19930129
WO	9411387	A2	19940526	WO 1993-US10659	19931105
WO	9411387	A3	19940929		
	W: BB, BG, BR, BY, CZ, FI, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ				
	RW: BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
RU	2120445	C1	19981020	RU 1995-112521	19931105
RO	115164	B1	19991130	RO 1995-940	19931105
RO	115165	B1	19991130	RO 1999-785	19931105
CZ	287842	B6	20010214	CZ 1995-1268	19931105
SK	281765	B6	20010710	SK 1995-659	19931105
PL	186740	B1	20040227	PL 1993-333738	19931105
IL	107574	A1	20000716	IL 1993-107574	19931111
IL	125769	A1	20030312	IL 1993-125769	19931111
IL	125770	A1	20040219	IL 1993-125770	19931111
EP	599376	A2	19940601	EP 1993-203163	19931112
EP	599376	A3	19940928		
EP	599376	B1	19980408		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
EP	655458	A2	19950531	EP 1995-200270	19931112
EP	655458	A3	19960710		
EP	655458	B1	19990303		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
EP	823436	A2	19980211	EP 1997-201712	19931112
EP	823436	A3	19981125		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
AT	164850	E	19980415	AT 1993-203163	19931112
ES	2052476	T3	19980616	ES 1993-203163	19931112
AT	177112	E	19990315	AT 1995-200270	19931112
ES	2072848	T3	19990501	ES 1995-200270	19931112
CA	2103107	AA	19940520	CA 1993-2103107	19931115
AU	9350787	A1	19940616	AU 1993-50787	19931118
AU	658774	B2	19950427		
JP	06199889	A2	19940719	JP 1993-289536	19931118
JP	07110875	B4	19951129		
~~ZA~~	~~9308620~~	~~A~~	~~19940804~~	~~ZA 1993-8620~~	~~19931118~~
HU	66973	A2	19950130	HU 1993-3275	19931118
HU	216195	B	19990528		
JP	09235294	A2	19970909	JP 1996-259373	19931118
HR	931410	B1	20000630	HR 1993-931410	19931118
CN	1090583	A	19940810	CN 1993-114530	19931119
CN	1058018	B	20001101		
US	5652365	A	19970729	US 1995-411685	19950330
FI	9502422	A	19950518	FI 1995-2422	19950518
NO	9501986	A	19950519	NO 1995-1986	19950519
US	5886184	A	19990323	US 1997-824426	19970326
HK	1008338	A1	20000505	HK 1998-109309	19980721
LV	12212	B	19990320	LV 1998-236	19981026
NO	9900468	A	19950519	NO 1999-468	19990201
NO	9902580	A	19950519	NO 1999-2580	19990528
LV	12460	B	20000920	LV 2000-26	20000223
HR	2000000295	A1	20000831	HR 2000-295	20000512
HR	20000295	B1	20020831		
FI	2001000289	A	20010215	FI 2001-289	20010215
FI	2001000290	A	20010215	FI 2001-290	20010215
FI	2004000559	A	20040421	FI 2004-559	20040421

PRIORITY APPLN. INFO.:

US 1992-978535	B2	19921119
US 1993-10734	A	19930129
WO 1993-US10659	W	19931105
IL 1993-107574	A3	19931111

	EP 1993-203163	A3 19931112
	JP 1993-289536	A3 19931118
	US 1995-411685	A3 19950330

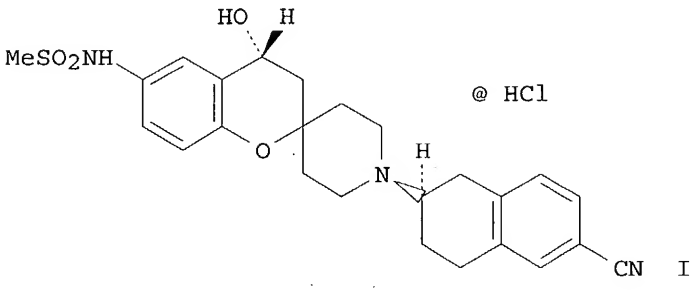
OTHER SOURCE(S): CASREACT 124:117692

AB Finasteride is prepared by treating a carboxylic ester analog with Me3CNH2 in presence of an organomagnesium halide, present in at least a 2:1 molar ratio to the ester. Two polymorphic **crystalline** forms of finasteride are also prepared Thus, Me 3-oxo-4-aza-5α-androst-1-en-17α-carboxylate was treated with Me3CNH2 and 2 mol of EtMgBr to give 97% finasteride.

L71 ANSWER 15 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:994313 HCAPLUS
DOCUMENT NUMBER: 124:86818
TITLE: Preparation and characterization of the different **crystal** forms of (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl)-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]yl]methanesulfonamide hydrochloride
INVENTOR(S): Desmond, Richard; Tschaen, David M.; McCauley, James A.; **Varsolona, Richard J.**
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9523146	A1	19950831	WO 1995-US2265	19950223
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9518820	A1	19950911	AU 1995-18820	19950223
PRIORITY APPLN. INFO.:			US 1994-201841	19940225
			WO 1995-US2265	19950223

GI



I

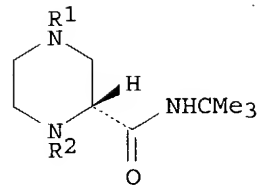
AB The 9 different morphol. forms of the antiarrythmic (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl)-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidinyl]yl]methanesulfonamide hydrochloride (I) are

prepared by selective **crystallization** or precipitation and characterized.

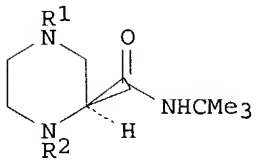
L71 ANSWER 16 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:994187 HCAPLUS
DOCUMENT NUMBER: 124:55978
TITLE: Process for making HIV protease inhibitors containing N-tert-butyl-2-piperazinecarboxamide derivative
INVENTOR(S): Rossen, Kai; Askin, David; Reider, Paul; **Varsolona, Richard J.**; Volante, Ralph
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9521162	A1	19950810	WO 1995-US1232	19950130
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
TW 472047	B	20020111	TW 1995-84100727	19950127
CA 2180947	AA	19950810	CA 1995-2180947	19950130
AU 9516967	A1	19950821	AU 1995-16967	19950130
AU 691878	B2	19980528		
EP 741712	A1	19961113	EP 1995-908747	19950130
EP 741712	B1	20011004		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
HU 76303	A2	19970728	HU 1996-2143	19950130
JP 09508628	T2	19970902	JP 1995-520686	19950130
~~BR 9506727~~	~~A~~	~~19970923~~	~~BR 1995-6727~~	~~19950130~~
RU 2135482	C1	19990827	RU 1996-117468	19950130
SK 281861	B6	20010806	SK 1996-1006	19950130
AT 206407	E	20011015	AT 1995-908747	19950130
ES 2161863	T3	20011216	ES 1995-908747	19950130
RO 118292	B1	20030430	RO 1996-1576	19950130
CZ 291774	B6	20030514	CZ 1996-2272	19950130
US 5663341	A	19970902	US 1995-487903	19950607
FI 9603054	A	19960801	FI 1996-3054	19960801
PRIORITY APPLN. INFO.:			US 1994-192916 A	19940204
			WO 1995-US1232 W	19950130

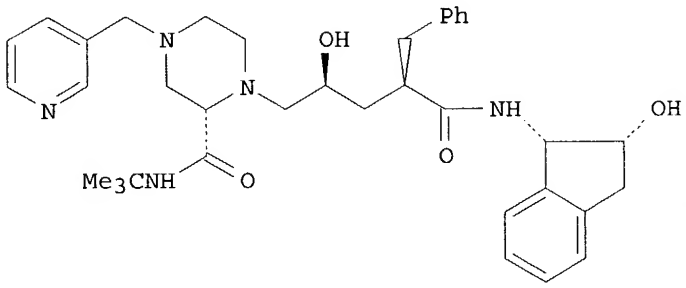
OTHER SOURCE(S): MARPAT 124:55978
GI



I



II



III

AB A process for racemization of optically pure or enriched piperazine-2-tert-butylcarboxamide and its derivs. (I or II; R1, R2 = H R, COR, CO2R; wherein R = C1-5 alkyl, arylmethyl, heteroarylmethyl, aryl, CF3) comprises reacting the optically pure or enriched piperazine compound with a racemizing agent selected from a strong base, an anhydrous metal salt or a carboxylic acid, in a solvent at a temperature range of between room temperature and 250°. The piperazine carboxamide derivs. are key intermediates in the preparation of HIV protease inhibitor compds., including Compound J (III).

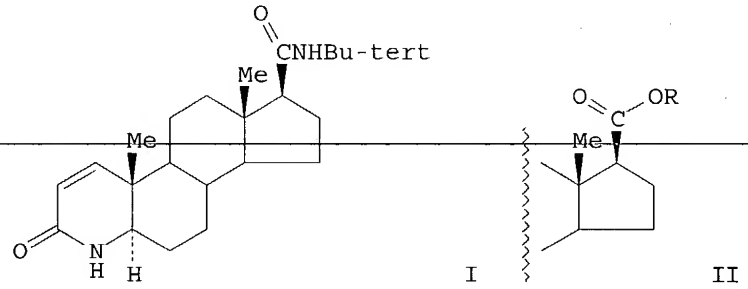
Thus, 0.21 mol L-pyroglutamic acid and 5 mL H2O were added to a solution of 0.11 mol (RS)-2-(tert-butylcarboxamido)piperazine in 155 mL n-propanol and the resulting slurry was heated to reflux to give a homogeneous yellow solution which was cooled to 50°, seeded with (R)-2-(tert-butylcarboxamido)piperazine.L-pyroglutamic acid salt (IV), cooled to 25°, aged for 16 h, and filtered to give, after washing with 35 mL cold n-propanol/1% H2O, 48% IV of 98% e.e. The yellow mother liquor containing 46% (S)-2-(tert-butylcarboxamido)piperazine.L-pyroglutamic acid salt were evaporated to give the salt which (50.1 mmol) was dissolved in 226 mL n-propanol and 35.5 mL Et3N and treated with a solution of 50.1 mmol Boc2O in 24 mL EtOAc over 2 h to give, after workup and **crystallization**, S-isomer II (R1 = Boc, R2 = H) (V) of >99.9% e.e. The R-isomer salt IV (0.468 mol) was treated with a mixture of 80 mL 50% NaOH, 700 mL H2O, and 40 mL n-propanol to give R-isomer I (R1 = R2 = H) (VII), which was heated and racemized with Me3COK in a mixture of cyclohexane and THF to reflux for 7 h, cooled to 2° for 2 h, and filtered to give, after washing with cyclohexane and drying, a white **crystalline** powder containing 50.8% R-isomer VII and 49.2% S-isomer II (R1 = R2 = H) (VIII). This racemate can be similarly resolved to give the desired S-isomer VIII. The S-isomer V was converted into Compound J III in 4 steps.

L71 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:557962 HCAPLUS
DOCUMENT NUMBER: 121:157962
TITLE: A process for the production of finasteride and its polymorphs
INVENTOR(S): Dolling, Ulf H.; McCauley, James A.; **Varsolona,**

Richard J.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 599376	A2	19940601	EP 1993-203163	19931112
EP 599376	A3	19940928		
EP 599376	B1	19980408		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5468860	A	19951121	US 1993-10734	19930129
EP 655458	A2	19950531	EP 1995-200270	19931112
EP 655458	A3	19960710		
EP 655458	B1	19990303		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
EP 823436	A2	19980211	EP 1997-201712	19931112
EP 823436	A3	19981125		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				

PRIORITY APPLN. INFO.: US 1992-978535 A 19921119
US 1993-10734 A 19930129
EP 1993-203163 A3 19931112
OTHER SOURCE(S): CASREACT 121:157962; MARPAT 121:157962
GI



I

II

AB The 5α-reductase inhibitor finasteride (I) is prepared by reaction of 17β-carboalkoxy-4-aza-5α-androst-1-en-3-ones II [R = C1-10 linear, branched, or cyclic alkyl with optional Ph substituent(s)], as their Mg halide salts, with t-butylaminomagnesium halide, present in at least a 2:1 molar ratio to II, formed from tert-BuNH2 and an aliphatic/aryl magnesium halide at ambient temperature in an inert organic solvent under an inert atmospheric, followed by heating and recovering I. In 2 examples using II (R = Me), EtMgBr, and tert-BuNH2, under N in refluxing THF (12 h), I was prepared in 97% yield. Also disclosed are 2 polymorphic **crystalline** forms of I, and methods of their production Dissolving I in glacial AcOH and adding H2O up to ≥84 weight% H2O gives form I, whereas adding H2O up to 75-80 weight% H2O gives form II.

L71 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:633857 HCAPLUS
DOCUMENT NUMBER: 119:233857

TITLE: The effect of polymorphism and metastability on the characterization and isolation of two pharmaceutical compounds
AUTHOR(S): McCauley, J. A.; **Varsolona, R. J.**; Levorse, D. A.
CORPORATE SOURCE: Merck Res. Lab., Rahway, NJ, 07065, USA
SOURCE: Journal of Physics D: Applied Physics (1993), 26(8B), B85-B89
CODEN: JPAPBE; ISSN: 0022-3727
DOCUMENT TYPE: Journal
LANGUAGE: English

AB L-706,000, a class III antiarrhythmic compound, exists in several different **crystalline** structures including two anhydrous polymorphs, two dihydrated enantiotropic polymorphs, a monohydrate and several organic solvent solvates. The isolation of the desired **crystal** modification, dihydrate type A, can be accomplished under thermodn. or kinetic control depending on the conditions. Under kinetic control, the isolation depends on a suspended transformation of a metastable state. L-700,462, a thrombotic agent, exists in three **crystalline** structures: a monohydrate and two anhydrous monotropic polymorphs. Both anhydrous polymorphs, when hydrated, yielded the single monohydrate. Drying of the monohydrate, depending on the conditions and sample, will give either anhydrous form. The varying results obtained upon drying are, once again, indicative of the presence of metastable states and suspended transformations in connection with the solid state of L-700,462.

L71 ANSWER 19 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:534506 HCAPLUS
DOCUMENT NUMBER: 113:134506
TITLE: Contact nuclei formation in aqueous dextrose solutions
AUTHOR(S): **Cerreta, Michael K.**; Berglund, Kris A.
CORPORATE SOURCE: Dep. Chem. Eng., Michigan State Univ., East Lansing, MI, 48824, USA
SOURCE: Journal of Crystal Growth (1990), 102(4), 869-76
CODEN: JCRGAE; ISSN: 0022-0248
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A laser Raman microprobe was used in situ to observe the growth of alpha dextrose monohydrate on alpha anhydrous dextrose **crystals.** The Raman spectra indicated growth of the monohydrate below 28.1°, but the presence of only the anhydrous form above 40.5°. Contact nucleation expts. with parent anhydrous **crystals** yielded only monohydrate nuclei below 28.1°, whereas contacts in solns. between 34.5 and 41.0° produced both **crystalline** forms, and contacts in solns. above 43.5° produced only anhydrous nuclei. The inability of the monohydrate to grow on anhydrous **crystals** in the same solution that formed the two **crystalline** phases with a single contact precluded a simple attrition mechanism of nuclei formation. For the same reason, the hypothetical mechanism involving parent **crystal** stabilization of pre-**crystalline** of pre-**crystalline** clusters, allowing the clusters to grow into nuclei, was also contradicted. A third, mechanism, which might be a combination of the two, was believed to apply.

L71 ANSWER 20 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1988:83139 HCAPLUS
DOCUMENT NUMBER: 108:83139
TITLE: The structural effects of pH on concentrated aqueous ammonium dihydrogen phosphate by laser Raman spectroscopy

AUTHOR(S): **Cerreta, Michael K.**; Berglund, Kris A.
CORPORATE SOURCE: Dep. Chem. Eng., Michigan State Univ., East Lansing, MI, 48824, USA
SOURCE: Cryst. Precip., Proc. Int. Symp. (1987), 53-9. Editor(s): Strathdee, Graeme L.; Klein, M. O.; Melis, L. A. Pergamon: Oxford, UK. CODEN: 56FAAU
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The structure of pure, concentrated aqueous solns. of dihydrogen orthophosphates is composed of "free" and H-bonded anions. The influence of pH on the structure of ammonium dihydrogen phosphate solns. from pH 3.8 to 5.0 was investigated by laser Raman spectroscopy. Except for the appearance of the (OH)P-O3 sym. stretching vibration, the spectra show little evidence of structural breakup that could account for the increased ease of **crystal** growth at the higher pH.

L71 ANSWER 21 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1988:12218 HCAPLUS
DOCUMENT NUMBER: 108:12218
TITLE: The structure of aqueous solutions of some dihydrogen orthophosphates by laser Raman spectroscopy
AUTHOR(S): **Cerreta, Michael K.**; Berglund, Kris A.
CORPORATE SOURCE: Dep. Chem. Eng., Michigan State Univ., East Lansing, MI, 48824, USA
SOURCE: Journal of Crystal Growth (1987), 84(4), 577-88 CODEN: JCRGAE; ISSN: 0022-0248
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Laser Raman studies at 700-1350 cm-1 for powdered **crystals** and 0.01 M to saturated aqueous MH2PO4 (M = NH4, Na, K) showed that the 875 cm-1 P(OH)2 sym. stretch band intensity increased as solute concentration increased and that an extreme asym. developed toward lower energy in the 1075 cm-1 P:O2 sym. stretch band, while the integrated intensity ratio (875/1075 cm-1 band) remained constant These results indicate anion-anion H bonding. Deconvolution of spectral bands showed that only 40 and 20% of the H2PO4- exists as monomers in KH2PO4 or (NH4)H2PO4 solns., resp., and that anion association does not cease at the dimer stage. There was no evidence for quasi-**crystalline** species in solution Rapid z-direction growth, growth activation energy, and the rate-limiting surface growth mechanism can be explained in terms of breaking and reforming of H bonds during the growth process.

L71 ANSWER 22 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1985:53233 HCAPLUS
DOCUMENT NUMBER: 102:53233
TITLE: Raman spectroscopic studies of the structure of supersaturated ammonium dihydrogen phosphate solutions
AUTHOR(S): **Cerreta, M. K.**; Berglund, K. A.
CORPORATE SOURCE: Dep. Chem. Eng., Iowa State Univ., Ames, IA, USA
SOURCE: Process Technology Proceedings (1984), 2(Ind. Cryst.), 233-6 CODEN: PTPREM; ISSN: 0921-8610
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Raman spectroscopic studies of quiescent undersatd. and supersatd. NH4H2PO4 aqueous solns. were performed on the ν1 (totally sym. or breathing mode) and ν3 (sym. twist) H2PO4- bands as well as for the ν1 band of

solid NH4H2PO4 and solid (NH4)2HPO4. The splitting of the nondegenerate NH4H2PO4 ν1 band in concentrated solution is interpreted in terms of a well-ordered **quasicryst.** solution structure. Increases in ν1 half-width at half-height support this view. Changes in the ν3 band suggest future avenues of investigation.

L71 ANSWER 23 OF 25 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1997:324157 BIOSIS
DOCUMENT NUMBER: PREV199799623360
TITLE: The polarizing microscope in pharmaceutics.
AUTHOR(S): **Smoliga, John A.**
CORPORATE SOURCE: **Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA**
SOURCE: Scanning, (1997) Vol. 19, No. 3, pp. 194.
Meeting Info.: Proceedings of SCANNING 97. Monterey, California, USA. April 20, 1997.
CODEN: SCNNDF. ISSN: 0161-0457.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Aug 1997
Last Updated on STN: 5 Aug 1997

L71 ANSWER 24 OF 25 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1994-0139321 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 1994 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): The effect of polymorphism and metastability on the characterization and isolation of two pharmaceutical compounds
Crystal growth of organic materials
AUTHOR: MCCAULEY J. A.; **VARSOLONA R. J.**; LEVORSE D. A.
PUGH David (ed.); ROBERTS Kevin (ed.); SHERWOOD John N. (ed.)
CORPORATE SOURCE: Merck Research Laboratories, Rahway NJ 07065, United States
Univ. Strathclyde, Glasgow, United Kingdom
SOURCE: Journal of physics. D. Applied physics, (1993), 26(8B), B85-B89, 8 refs.
Conference: 2 CGOM-2. International workshop, Glasgow (United Kingdom), 7 Sep 1992
ISSN: 0022-3727 CODEN: JPAPBE
DOCUMENT TYPE: Journal; Conference
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-5841, 354000035404090120
AN 1994-0139321 PASCAL
CP Copyright .COPYRGT. 1994 INIST-CNRS. All rights reserved.
AB L-706,000, a class III antiarrhythmic compound, has been found to exist in several different **crystalline** structures including two anhydrous polymorphs, two dihydrated enantiotropic polymorphs, a monohydrate and several organic solvent solvates. The isolation of the desired **crystal** modification, dihydrate type A, can be accomplished under thermodynamic or kinetic control depending on the conditions. Under kinetic control, the isolation depends on a suspended transformation of a metastable state. L-700,462, a thrombotic agent, has

been found to exist in three **crystalline** structures: a monohydrate and two anhydrous monotropic polymorphs

L71 ANSWER 25 OF 25 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002383086 EMBASE
TITLE: Erratum: A spectroscopic and **crystallographic** study of polymorphism in an aza-steroid (Journal of Pharmaceutical Sciences (2000) 89:10 (1271-1285)).
AUTHOR: Wenslow R.M.; Baum M.W.; Ball R.G.; McCauley J.A.; **Varsolona R.J.**
CORPORATE SOURCE: R.M. Wenslow, Merck Research Laboratories, 126 E. Lincoln Avenue, Rahway, NJ 07065-0900, United States
SOURCE: Journal of Pharmaceutical Sciences, (1 Nov 2002) 91/11 (2465).
ISSN: 0022-3549 CODEN: JPMSAE
COUNTRY: United States
DOCUMENT TYPE: Journal; Errata
FILE SEGMENT: 039 Pharmacy
LANGUAGE: English

=> FIL STNGUIDE

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 8, 2004 (20041008/UP).

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